Supplemental File S2 – Heme Biosynthesis

Synthesis of heme is critical to hemoglobin formation and oxygen transport. In a normal man, 6.3 g of hemoglobin is replaced daily with little wastage; porphyrias result from disruption of synthesis or feedbacks in process control, often due to deficiency of one or more enzymes in the synthesis pathway (Rimington 1989). Defects in each of the eight enzymes in the heme biosynthetic pathway have been associated with a specific porphyria (Phillips 2019). We examined variation at nine genes (O'Malley *et al*. 2018) among sciurids.

The *ALAD* gene encodes aminolevulinate dehydratase. Diseases associated with *ALAD* include porphyria, and acute hepatic porphyria. Among its related pathways are porphyrin and innate immune system response. The ALAD enzyme is composed of eight identical subunits and catalyzes the condensation of two molecules of δ-aminolevulinate to form porphobilinogen (a precursor of heme). *ALAD* catalyzes the second step in the porphyrin and heme biosynthetic pathway. ALAD enzymatic activity is inhibited by lead and a defect in the *ALAD* structural gene can cause increased sensitivity to lead poisoning and acute hepatic porphyria. Alternative splicing of this gene results in multiple transcript variants encoding different isoforms.

Our sequence alignment included 355 predicted amino acids for *S. niger*. There were differences at 16 amino acids among *Sciurus* species; additionally, *S. vulgaris* lacked 23 amino acids at positions 270-293. Three ground squirrels – *S. dauricus*, *I. tridecemlineatus*, and *U. parryii* - had a 32-amino acid sequence at positions 140-172 not seen in other species.

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Alad             MHHQSVLHSGYFHPLLRSWQTAASTVSASNLIYPIFVTDVPDDVQPIASLPGVARYGVNQ
Aplodontia_rufa  MQPQSILHSGYFHPLLRTWQTAATTLSASNLIYPIFVT-VSKN-GPDLSAQGGGRCGTGQ
Xerus_inauris@A  MQPQSVLHSGYFHPLLRTWQAAATSLSASNFIYPIFVT-VPRNVQPIASLPGVARYGVNQ
Marmota_monax@A  MQPQSVLHSGYFHPLLRTWQTAATTLSASNFIYPIFVT-VPDDPASPQSLPSPPRYGVNR
Spermophilus_da  MQPQSVLHSGYFHPLLRTWQTAATTLSASNFIYPIFVT-VPRN-GPDLSVHGGGRYGVNQ
Ictidomys_tride  MQPQSVLHSGYFHPLLRTWQTAATTLSASNFIYPIFVT-VPDDVQPPQSLPSPPRYGVNR
Urocitellus_par  MQPQSVLHSGYFHPLLRTWQTAATTLSASNFIYPIFVT-VPRNVQPPQSLPSPPRYGVNR
Sciurus_vulgari  MQPQSVLHSGYFHPLLRTWQTAATTLSASNFIYPIFVTDVPDDIQPIASLPVMARYRVNR
Sciurus_carolin  MQPQSVLHSGYFHPLLRTWQTAATTLSASNFIYPIFVTDVPDDIQPIASLPGMSRYGVNQ
Sciurus_niger@A  MHPQSVLHSGYFHPLLRTWQTAATTLSASNFIYPIFVTDVPDDIQPIANLPGMSRYGVNQ
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Alad             LEEMLRPLVEAGLRCVLIFGVPSRVPKDEQGSAADSEDSPTIEAVRLLRKTFPSLLVACD
Aplodontia_rufa  LEEMLRPLVEAGLRCVLIFGVPSRVPKDERGSAADSEESPAIEAIRLLRKTFPNLLVACD
Xerus_inauris@A  LEEMLRPLVEAGLRCVLIFGVPSRVP-DERGSAADSEESPAIEAIRLLRKTFPSLLVACD
Marmota_monax@A  LEEMLKPLVEEGLRCVLIFGVPSRVPKDEQGSAADSEESPTIEAVRLLRKTFPSLLVACD
Spermophilus_da  LEEMLRPLVEAGLRCVLIFGVPSRCP-DERGSAADSEESPTIEAVRLLRKTFPSLLVACD
Ictidomys_tride  LEEMLKPLVEEGLRCILIFGVPSRVPKDEQGSAADSEESPTIEAVRLLRKTFPSLLVACD
Urocitellus_par  LEEMLKPLVEEGLRCVLVFGVPSRVPKDEQGSAADSEESPTIEAVRLLRKTFPSLLVACD
Sciurus_vulgari  LEEMLRPLVEEGLCCVLIFGVPSKVPKDERGSAADSEKSPAIEAIRLLRKTFPNLLVACD
Sciurus_carolin  LEEMLRPLVEAGLRCVLIFGVPSRVPKDERGSAADSEKSPAIEAIHLLRKTFPNLLVACD
Sciurus_niger@A  LEEMLRPLVEAGLRCVLIFGVPSRVPKDERGSAADSEDSPTIEAVRLLRKTFPNLLVACD
                 *****:**** ** *:*:*****: * **:*******.**:***::*******.******

Alad             VCLCPYTSHGHCGLLSENGAFLAEESRQRLAEVALAYAKA-------------------
Aplodontia_rufa  VCLCPYTSHGHCGLLSENGAFRAEESRQRLAEVALAYAKA-------------------
Xerus_inauris@A  VCLCPYTSHGHCGLLSENGAFRAEESRQRLAEVALAYAKA-------------------
Marmota_monax@A  VCLCPYTSHGHCGLLSENGAFKAEESRQRLAEVALAYAKA-------------------
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Spermophilus_da   VCLCPYTSHGHCGLLSENGAFKAEESRQRLAEVALAYAKAGEVPRRGGHLWVGELAEWIE
Ictidomys_tride   VCLCPYTSHGHCGLLSENGAFKAEESRQRLAEVALAYAKAGEVPSRGGHLWVGELAEWIE
Urocitellus_par   VCLCPYTSHGHCGLLSENGAFKAEESRQRLAEVALAYAKAGEVPSRGGHLWVGELAEWIE
Sciurus_vulgari   ICLCPYTSHGHCGLLSENGAFRAEESRQRLAEVALAYAKA--------------------
Sciurus_carolin   ICLCPYTSHGHCGLLSENGAFRAEESRQRLAEVALAYAKA--------------------
Sciurus_niger@A   ICLCPYTSHGHCGLLSENGAFRAEESRQRLAEVALAYAKA--------------------
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Alad              ------------GCQVVAPSDMMDGRVEAIKAALLKHGLGNRVSVMSYSAKFASCFYGPF
Aplodontia_rufa   ------------GAQVVAPSDMMDGRVEAIKAALLKHGLGNRVSVMSYSAKFASCFYGPF
Xerus_inauris@A   ------------GCQVVAPSDMMDGRVEAIKEALMAHGLGNRVSVMSYSAKFASCFYGPF
Marmota_monax@A   ------------GCQVVAPSDMMDGRVEAIKEALMAHGLGNRVSVMSYSAKFASCFYGPF
Spermophilus_da   GPRVLKTTLCPSGCQVVAPSDMMDGRVEAIKDALMAHGLGNRVSVMSYSAKFASCFYGPF
Ictidomys_tride   GPRVLKTSLCPSGCQVVAPSDMMDGRVEAIKDALMAHGLGNRVSVMSYSAKFASCFYGPF
Urocitellus_par   GPRVLKTTLCPSGCQVVAPSDMMDGRVEAIKDALLAHGLGNRVSVMSYSAKFASCFYGPF
Sciurus_vulgari   ------------GCQVVAPSDMMDGRVEAIKEALMAHGLGNRVSVMSYSAKFASCFYGPF
Sciurus_carolin   ------------GCQVVAPSDMMDGRVEAIKEALMAHGLGNRVSVMSYSAKFASCFYGPF
Sciurus_niger@A   ------------GCQVVAPSDMMDGRVEAIKEALMAHGLGNRVSVMSYSAKFASCFYGPF
                              * .***************** **: **********************

Alad              RDAAQSSPAFGDRRCYQLPPGARGLALRAVA----------------------------
Aplodontia_rufa   RDAAQSSPAFGDRRCYQLPPGARGLALRAVA----------------------------
Xerus_inauris@A   RDAAQSSPAFGDRRCYQLPPGARGLALRAVVNDQAA---------THTHPLPA----YPL
Marmota_monax@A   RDAAQSSPAFGDRRCYQLPPGARGLALRAVA----------------------------
Spermophilus_da   RDAAQSSPAFGDRRCYQLPPGARGLALRAVVSDQAD-------THTHTHTLPA----CPF
Ictidomys_tride   RDAAQSSPAFGDRRCYQLPPGARGLALRAVVSDQAADTHTHTYTHTHTHTLPA----CPF
Urocitellus_par   RDAAQSSPAFGDRRCYQLPPGARGLALRAVA----------------------------
Sciurus_vulgari   QDAALSSPTFGDSCCYQLPPGARGLALQAV-----------------------------
Sciurus_carolin   RDAAQSSPAFGDRRCYQLPPGARGLALRAVVSDQAA---------THSPPCLSPSRINAV
Sciurus_niger@A   RDAAQSSPAFGDRRCYQLPPGARGLALRAVVSDQAA---------THSPPCLSPSRINAV
                  :*** ***:***   **************:**

Alad              ---------RDIQEGADMLMVKPGLPYLDMV-REVKDKHPELPLAVYQVSGEFAMLWHGA
Aplodontia_rufa   ---------RDIQEGADMLMVKPGLPYLDMV-REVKDQHPELPLAVYHVSGEYAMLWHGA
Xerus_inauris@A   PRHCTLIPDRDVREGADMLMVKPGMPYLDIV-REVKDKHPELPLAVYHVSGEFAMLWHGA
Marmota_monax@A   ---------RDIQEGADMLMVKPGLPYLDMV-REVKDQHPQLPLAVYHVSGEFAMLWHGA
Spermophilus_da   PRHFTLFPDRDVREGADMLMVKPGLPYLDMV-REVKDKHPQLPLAVYHVSGEFAMLWHGA
Ictidomys_tride   PRHFTLFPDRDVREGADMLMVKPGMPYLDIV-REVKDKHPQLPLAVYHVSGEFAMLWHGA
Urocitellus_par   ---------RDIQEGADMLMVKPGLPHLNPVPMAASPQHPQLPLAVYHVSGEFAMLWHGA
Sciurus_vulgari   --------DRDVQEGADMLMVKPGMPYLDIV-WEVKDKHPELPLAVYHVSGEFAMLWHGA
Sciurus_carolin   VRHFTFIPDRDVQEGADMLMVKPGMPYLDIV-REVKDKHPELPLAVYHVSGEFAMLWHGA
Sciurus_niger@A   VRHFTLIPDRDVQEGADMLMVKPGMPYLDIV-REVKDKHPELPLAVYHVSGEFAMLWHGA
                           **::***********:*:*: *    .. :**:******:****:*******

Alad              QAGAFDLRTAVLETMTAFRRAGADIIITYFAPQLLKWLKEEZ
Aplodontia_rufa   RAGAFDLKAAVLEAMTAFRRAG--------------------
Xerus_inauris@A   RAGAFDLKAAVLEAMTAFRRAG--------------------
Marmota_monax@A   RAGAFDLKAAVLEAMTAFRRAG--------------------
Spermophilus_da   RAGAFDLKAAVLEAMTAFRRAG--------------------
Ictidomys_tride   RAGAFDLKAAVLEAMTAFRRAG--------------------
Urocitellus_par   RAGAFDLKAAVLEAMTAFRRAG--------------------
Sciurus_vulgari   QAGAFDLKAAVLEAMTAFRRAGADVIITYHTPQLLQWLKE--
Sciurus_carolin   QAGAFDLKAAVLEAMTAFRRAGADIIITYYTPQLLQWLKE--
Sciurus_niger@A   QAGAFDLKAAVLEAMTAFRRAGADIIITYYTPQLLRWLKE--
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ALAS1 encodes 5'-aminolevulinate synthase 1. Diseases associated with *ALAS1* include acute porphyria and anemia, sideroblastic, 1. Among its related pathways are porphyrin and glycine, serine, and threonine metabolism. Gene ontology (GO) annotations related to this gene include pyridoxal phosphate binding and 5-aminolevulinate synthase activity. An important paralog of this gene is ALAS2. This gene encodes the mitochondrial enzyme which is catalyzes the rate-limiting step in heme (iron-protoporphyrin) biosynthesis. The enzyme encoded by this gene is the housekeeping enzyme; a separate gene encodes a form of the enzyme that is specific for erythroid tissue. The level of the mature encoded protein is regulated by heme; high levels of heme down-regulate the mature enzyme in mitochondria, while low heme levels up-regulate it. Alternative splicing results in multiple transcript variants encoding different isoforms.

The *ALAS1* amino acid sequence was rather highly conserved among sciurids and among all species considered. Among 640 amino acids for *Sciurus* species, we observed three point differences. The human sequence had a two-amino acid insertion at sites 84-85.

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Alas1            METVVRRCPFLSRVPQAFLQKAGKSLLFYAQNCPKMMEVGAKPAPRTLSTSAVHCQQVKE
Aplodontia_rufa  METVVRRCPFLSRVPQAFLQKAGKSLLFYAQNCPKMMEVWSKPVPRALTTSAVHCQQIKE
Xerus_inauris@A  METVVRRCPFLSRVPQAFLQKAGKSLLFYAQNCPKMMEIGSKPAPRALSTSAVHCQQIKE
Marmota_monax@A  METVVRRCPFLSRVPQAFLQKAGKSLLFYAQNCPKMMEVGSKPVPRAVSTSAVHCQQIKE
Spermophilus_da  METVVRRCPFLSRVPQAFLQKAGKSLLFYAQNCPKMMEVGSKPVPRAVSTSAVHCQQIKE
Ictidomys_tride  METVVRRCPFLSRVPQAFLQKAGKSLLFYAQNCPKMMEVGSKPVPRAVSTSAVHCQQIKE
Urocitellus_par  METVVRRCPFLSRVPQAFLQKAGKSLLFYAQNCPKMMEVGSKPVPRAVSTSAVHCQQIKE
Sciurus_vulgari  METVVRRCPFLSRVPQAFLQKAGKSLLFYAQNCPKMMEVGSKPAPRALSTSAVHCQQIKE
Sciurus_carolin  METVVRRCPFLSRVPQAFLQKAGKSLLFYAQNCPKMMEVGSKPAPRALSTSAVHCQQIKE
Sciurus_niger@A  METVVRRCPFLSRVPQAFLQKAGKSLLFYAQNCPKMMEVGSKPAPRALSTSAVHCQQIKE
                 *****************************************:  :**.**::.*********:**

Alas1            TPPANEKEKTAKAAVQQAPDESQMAQTPDGTQLPSGHPSPATSQGSGSKCPFLAAQLSQT
Aplodontia_rufa  TPPAGEEDKTAKAKVQETPDRSQ--QTPNGTQLPSAHLSPAMSQGTSSKCPFLAAQMSQT
Xerus_inauris@A  TPPASEEDKTAKTKVQQAPDRSQ--QTPNGMQLPSGHPLPAMSQGTASKCPFLAAQMSQT
Marmota_monax@A  TPPASEEDKTAKAKVQQAPDRSQ--QTPNGTQLPSGHHSPAMSQGTASKCPFLAAQMSQT
Spermophilus_da  TPPASEEDKTAKAKVQQAPDRSQ--QTPNGTQLPSGHHSPAMSQGTASKCPFLAAQMSQT
Ictidomys_tride  TPPASEEDKTAKAKVQQAPDRSQ--QTPNGTQLPPGHHSPAMSQGTASKCPFLAAQMSQT
Urocitellus_par  TPPASEEDKTAKAKVQQAPDRSQ--QTPNGTQLPSGHHSLAMSQGTASKCPFLAAQMSQT
Sciurus_vulgari  TPPASEDKTANKSKVQQAPDRSQ--QTPNGTQLPSGHPSPAMSQGTASKCPFLAAQMSQT
Sciurus_carolin  TPPASEDKTANKSKVQEAPDRSQ--QTPNGTQLPSGHPSPAMSQGTASKCPFLAAQMSQT
Sciurus_niger@A  TPPASEDKTANKSKVQQAPDRSQ--QTPNGTQLPSGHPSPAVSQGTASKCPFLAAQMSQT
                 ****.*...: *: **::**.**   ***:* ***..*   * ***:.*********:***

Alas1            GSSVFRKASLELQEDVQEMHAVRKEAAQSPVPPSLVNVKTDGEDPSRLLKNFQDIMRKQR
Aplodontia_rufa  GSSVFCKASLELQEDVQEMHAVRKEVAQTSVKPTVINVKTNGDDPSGLLKNFQDIMRKQR
Xerus_inauris@A  GSNVFCKASLELQEDVQEMHAVRKEVAQTSVNPSVISVKTDGKDPSELLKNFQDIMQKQR
Marmota_monax@A  GSNVFCKASLELQEDVQEMHAVRKEVAQTSVNPNVINVKTDGEDPSELLKNFQDIMRKQR
Spermophilus_da  GSNVFCKASLELQEDVQEMHAVRKEVAQTSVNPNVINVKTDGEDPSELLKNFQDIMRKQR
Ictidomys_tride  GSNVFCKASLELQEDVQEMHAVRKEVAQTSVNPNVINVKTDGEDPSELLKNFQDIMRKQR
Urocitellus_par  GSNVFCKASLELQEDVQEMHAVRKEVAQTSVNPNVINVKTDGEDPSELLKNFQDIMRKQR
Sciurus_vulgari  GSSVFCKASLELQEDVQEMHAVRKEVAQTSVNPNVISVKTDGEDPNELLKNFQDIMRKQR
Sciurus_carolin  GSSVFCKASLELQEDVQEMHAVRKEVAQTSVNPSVISVKTDGEDPNELLKNFQDIMRKQR
Sciurus_niger@A  GSSVFCKASLELQEDVQEMHAVRKEVAQTSVNPNVISVKTDGEDPNELLKNFQDIMRKQR
                 **.** *******************.**:.* *.::.***:*.**. *********:***

Alas1            PERVSHLLQDNLPKSVSTFQYDHFFEKKIDEKKNDHTYRVFKTVNRRAQIFPMADDYTDS
Aplodontia_rufa  PERVSHLLQDNLPKSVSTFQYDHFFEKKIDEKKNDHTYRVFKTVNRRAQIFPMADDYSDS
Xerus_inauris@A  PERVSHLLQDNLPKSVSTFQYDHFFEKKIDEKKNDHTYRVFKTVNRRAQIFPMADDYSDS
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Marmota_monax@A    PERVSHLLQDNLPKSVSTFQYDHFFEKKIDEKKNDHTYRVFKTVNRRAQIFPMADDYSDS
Spermophilus_da    PERVSHLFQDNLPKSVSTFQYDHFFEKKIDEKKNDHTYRVFKTVNRRAQIFPMADDYSDS
Ictidomys_tride    PERVSHLLQDNLPKSVSTFQYDHFFEKKIDEKKNDHTYRVFKTVNRRAQIFPMADDYSDS
Urocitellus_par    PERVSHLLQDNLPKSVSTFQYDHFFEKKIDEKKNDHTYRVFKTVNRRAQIFPMADDYSDS
Sciurus_vulgari    PERVSHLLQDNLPKSVSTFQYDHFFEKKIDEKKNDHTYRVFKTVNRRAQIFPMADDYSDS
Sciurus_carolin    PERVSHLLQDNLPKSVSTFQYDHFFEKKIDEKKNDHTYRVFKTVNRRAQIFPMADDYSDS
Sciurus_niger@A    PERVSHLLQDNLPKSVSTFQYDHFFEKKIDEKKNDHTYRVFKTVNRRAQIFPMADDYSDS
                   *******:****************************************************:**

Alas1              LITKKQVSVWCSNDYLGMSRHPRVCGAVMETVKQHGAGAGGTRNISGTSKFHVELEQALA
Aplodontia_rufa    LITKKQVSVWCSNDYLGMSRHPRVCGAVMETVKQHGAGAGGTRNISGTSKFHVELEQELA
Xerus_inauris@A    LITKKQVSVWCSNDYLGMSRHPRVCGAVMETVKQHGAGAGGTRNISGTSKFHVELEQELA
Marmota_monax@A    LITKKQVSVWCSNDYLGMSRHPRVCGAVMETVKQHGAGAGGTRNISGTSKFHVELEQELA
Spermophilus_da    LITKKQVSVWCSNDYLGMSRHPRVCGAVVETLKQHGAGAGGTRNISGTSKFHVELEQELA
Ictidomys_tride    LITKKQVSVWCSNDYLGMSRHPRVCGAVMETVKQHGAGAGGTRNISGTSKFHVELEQELA
Urocitellus_par    LITKKQVSVWCSNDYLGMSRHPRVCGAVMETVKQHGAGAGGTRNISGTSKFHVELEQELA
Sciurus_vulgari    LITKKQVSVWCSNDYLGMSRHPRVCGAVMETVKQHGAGAGGTRNISGTSKFHVELERALA
Sciurus_carolin    LITKKQVSVWCSNDYLGMSRHPRVCGAVMETVKQHGAGAGGTRNISGTSKFHVELEQELA
Sciurus_niger@A    LITKKQVSVWCSNDYLGMSRHPRVCGAVMETVKQHGAGAGGTRNISGTSKFHVELERELA
                   ****************************:**:***********************:  **

Alas1              DLHGKDAALLFSSCFVANDSTLFTLAKMMPGCEIYSDSGNHASMIQGIRNSRVPKYIFRH
Aplodontia_rufa    DLHGKDAALLFSSCFVANDSTLFTLAKMMPGCEIYSDSGNHASMIQGIRNSRVPKYIFRH
Xerus_inauris@A    DLHGKDAALLFSSCFVANDSTLFTLAKMMPGCEIYSDSGNHASMIQGIRNSRVPKYIFRH
Marmota_monax@A    DLHGKDAALLFSSCFVANDSTLFTLAKMMPGCEIYSDSGNHASMIQGIRNSRVPKYIFRH
Spermophilus_da    DLHGKDAALLFSSCFVANDSTLFTLAKMMPGCEIYSDSGNHASMIQGIRNSRVPKYVFRH
Ictidomys_tride    DLHGKDAALLFSSCFVANDSTLFTLAKMMPGCEIYSDSGNHASMIQGIRNSRVPKYIFRH
Urocitellus_par    DLHGKDAALLFSSCFVANDSTLFTLAKMMPGCEIYSDSGNHASMIQGIRNSRVPKYIFRH
Sciurus_vulgari    DLHGKDAALLFSSCFVANDSTLFTLAKMMPGCEIYSDSGNHASMIQGIRNSRVPKYIFRH
Sciurus_carolin    DLHGKDAALLFSSCFVANDSTLFTLAKMMPGCEIYSDSGNHASMIQGIRNSRVPKYIFRH
Sciurus_niger@A    DLHGKDAALLFSSCFVANDSTLFTLAKMMPGCEIYSDSGNHASMIQGIRNSRVPKYIFRH
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Alas1              NDVNHLRELLQRSDPSVPKIVAFETVHSMDGAVCPLEELCDVAHEFGAITFVDEVHAVGL
Aplodontia_rufa    NDVNHLRELLQRSDPSVPKIVAFETVHSMDGAVCPLEELCDVAHEFGAITFVDEVHAVGL
Xerus_inauris@A    NDVNHLRELLQRSDPSVPKIVAFETVHSMDGAVCPLEELCDVAHEFGAITFVDEVHAVGL
Marmota_monax@A    NDVNHLRELLQRSDPSVPKIVAFETVHSMDGAVCPLEELCDVAHEFGAITFVDEVHAVGL
Spermophilus_da    NDVNHLRELLQRSDPSVPKIVAFETVHSMDGAVCPLEELCDVAHEFGAITFVDEVHAVGL
Ictidomys_tride    NDVNHLRELLQRSDPSVPKIVAFETVHSMDGAVCPLEELCDVAHEFGAITFVDEVHAVGL
Urocitellus_par    NDVNHLRELLQRSDPSVPKIVAFETVHSMDGAVCPLEELCDVAHEFGAITFVDEVHAVGL
Sciurus_vulgari    NDVNHLRELLQRSDPSVPKIVAFETVHSMDGAVCPLEELCDVAHEFGAITFVDEVHAVGL
Sciurus_carolin    NDVNHLRELLQRSDPSVPKIVAFETVHSMDGAVCPLEELCDVAHEFGAITFVDEVHAVGL
Sciurus_niger@A    NDVNHLRELLQRSDPSVPKIVAFETVHSMDGAVCPLEELCDVAHEFGAITFVDEVHAVGL
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Alas1              YGARGGGIGDRDGVMPKMDIISGTLGKAFGCVGGYIASTSLLIDTVRSYAAGFIFTTSLP
Aplodontia_rufa    YGARGGGIGDRDGVMPKMDIISGTLGKAFGCVGGYIASTSLLVDTVRSYAAGFIFTTSLP
Xerus_inauris@A    YGAQGGGIGDRDGVMPKMDIISGTLGKAFGCVGGYIASTSLLIDTVRSYAAGFIFTTSLP
Marmota_monax@A    YGARGGGIGDRDGVMPKMDIISGTLGKAFGCVGGYIASTSLLIDTVRSYAAGFIFTTSLP
Spermophilus_da    YGARGGGIGDRDGVMPKMDIISGTLGKAFGCVGGYIASTSLLIDTVRSYAAGFIFTTSLP
Ictidomys_tride    YGARGGGIGDRDGVMPKMDIISGTLGKAFGCVGGYIASTSLLIDTVRSYAAGFIFTTSLP
Urocitellus_par    YGARGGGIGDRDGVMPKMDIISGTLGKAFGCVGGYIASTSLLIDTVRSYAAGFIFTTSLP
Sciurus_vulgari    YGAQGGGIGDRDGVMPKMDIISGTLGKAFGCVGGYIASTSLLIDTVRSYAAGFIFTTSLP
Sciurus_carolin    YGAQGGGIGDRDGVMPKMDIISGTLGKAFGCVGGYIASTSLLIDTVRSYAAGFIFTTSLP
Sciurus_niger@A    YGAQGGGIGDRDGVMPKMDIISGTLGKAFGCVGGYIASTSLLIDTVRSYAAGFIFTTSLP
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Alas1               PMLLAGALESVRILKSSEGRALRRQHQRNVKLLRQMLMDAGLPVIHCPSHIIPVRVADAA
Aplodontia_rufa     PMLLAGALESVRILKSSEGRALRRQHQRNVKLMRQMLMDAGLPVIHCPSHIIPVRVADAA
Xerus_inauris@A     PMLLAGALESVRILKSSEGRALRRQHQRNVKLMRQMLMDAGLPVIHCPSHIIPVRVADAA
Marmota_monax@A     PMLLAGALESVRILKSSEGRALRRQHQRNVKLMRQMLMDAGLPVIHCPSHIIPVRVADAA
Spermophilus_da     PMLLAGALESVRILKSSEGRALRRQHQRNVKLMRQMLMDAGLPVIHCPSHIIPVRVADAA
Ictidomys_tride     PMLLAGALESVRILKSSEGRALRRQHQRNVKLMRQMLMDAGLPVIHCPSHIIPVRVADAA
Urocitellus_par     PMLLAGALESVRILKSSEGRALRRQHQRNVKLMRQMLMDAGLPVIHCPSHIIPVRVADAA
Sciurus_vulgari     PMLLAGALESVRILKSSEGRALRRQHQRNVKLMRQMLMDAGLPVIHCPSHIIPVRVADAA
Sciurus_carolin     PMLLAGALESVRILKSSEGRALRRQHQRNVKLMRQMLMDAGLPVIHCPSHIIPVRVADAA
Sciurus_niger@A     PMLLAGALESVRILKSSEGRALRRQHQRNVKLMRQMLMDAGLPVIHCPSHIIPVRVADAA
                    ********************************:***************************

Alas1               KNTEICDELMTRHNIYVQAINYPTVPRGEELLRIAPTPHHTPQMMNFFVEKLLVTWKRVG
Aplodontia_rufa     KNTEICDELMSRHNIYVQAINYPTVPRGEELLRIAPTPHHTPQMMNFFVEKLLVTWKRVG
Xerus_inauris@A     KNTEICDELMSRHNIYVQAINYPTVPRGEELLRIAPTPHHTPQMMNFFVEKLLVTWKRVG
Marmota_monax@A     KNTEICDELMSRHNIYVQAINYPTVPRGEELLRIAPTPHHTPQMMNFFVEKLLVTWKRVG
Spermophilus_da     KNTEICDELMSRHNIYVQAINYPTVPRGEELLRIAPTPHHTPQMMNFFVEKLLATWKRVG
Ictidomys_tride     KNTEICDELMSRHNIYVQAINYPTVPRGEELLRIAPTPHHTPQMMNFFVEKLLVTWKRVG
Urocitellus_par     KNTEICDELMSRHNIYVQAINYPTVPRGEELLRIAPTPHHTPQMMNFFVEKLLVTWKRVG
Sciurus_vulgari     KNTEICDELMSRHNIYVQAINYPTVPRGEELLRIAPTPHHTPQMMNFFVEKLLATWKRVG
Sciurus_carolin     KNTEICDELMSRHNIYVQAINYPTVPRGEELLRIAPTPHHTPQMMNFFVEKLLATWKRLG
Sciurus_niger@A     KNTEICDELMSRHNIYVQAINYPTVPRGEELLRIAPTPHHTPQMMNFFVEKLLATWKRVG
                    **********:*********************************************.****:*

Alas1               LELKPHSSAECNFCRRPLHFEVMSEREKAYFSGMSKMVSAQAZ
Aplodontia_rufa     LELKPHSSAECNFCRRPLHFEVMSEREKSYFSGMSKLVSAQA-
Xerus_inauris@A     LELKPHSSAECNFCRRPLHFEVMSEREKAYFSGMSKLVSAQA-
Marmota_monax@A     LELKPHSSAECNFCRRPLHFEVMSEREKSYFSGLSKLVSAQA-
Spermophilus_da     LELKPHSSAECNFCRRPLHFEVMSEREKSYFSGMSKLVSAQA-
Ictidomys_tride     LELKPHSSAECNFCRRPLHFEVMSEREKAYFSGMSKLVSAQA-
Urocitellus_par     LELKPHSSAECNFCRRPLHFEVMSEREKSYFSGMSKLVSAQA-
Sciurus_vulgari     LELKPHSSAECNFCRRPLHFEVMSEREKAYFSGMSKLVSAQA-
Sciurus_carolin     LELKPHSSAECNFCRRPLHFEVMSEREKAYFSGMSKLVSAQA-
Sciurus_niger@A     LELKPHSSAECNFCRRPLHFEVMSEREKAYFSGMSKLVSAQA-
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ALAS2 encodes 5'-aminolevulinate synthase 2. Diseases associated with *ALAS2* include anemia, sideroblastic, 1 and protoporphyria, erythropoietic, X-linked pyridoxine-responsive sideroblastic anemia. Among its related pathways are porphyrin and glycine, serine, and threonine metabolism. Gene ontology (GO) annotations related to this gene include pyridoxal phosphate binding and glycine binding. An important paralog of this gene is *ALAS1*. The product of this gene specifies an erythroid-specific mitochondrially located enzyme. The encoded protein catalyzes the first step in the heme biosynthetic pathway. Alternatively spliced transcript variants encoding different isoforms have been identified.

Among 586 amino acids, we observed three differences among *Sciurus* species at *ALAS2*. We noted an insertion of 15-16 amino acids at positions 61-76 in seven non-*Sciurus* sequences. *X. inauris* had an insertion of five amino acids at positions 554-559.

```
Alas2               MVAAAMLLRSCPVLSQGPTGLLGKVAKTYQFLFSIGRCPILATQGPTCSQIHLKATKAGG
Aplodontia_rufa     MVAAAVLLQCCPVLARGPTGLLGKVIKTHQFLFGTGRCPILAAQGPICSQIHLKATKAGG
Xerus_inauris@A     MVAAAMLLQCCPVLARGPTGLLGKVIKTHQFLFGTGRCPILATQGPICSQIHLKTTNAGG
Marmota_monax@A     MVAAAVLLQCCPVLARGPTGLLSKVVKTHQFLFGTGRCPILATQGPICSQIHLKATRAGG
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Spermophilus_da   MVAAAVLLQCCPVLARGPTGLLSKVVKTHQFLFGTGRCPILATQGPICSQIHLKATRAGG
Ictidomys_tride   MVAAAVLLQCCPVLARGPTGLLSKVIKTHQFLFGTGRCPILATQGPICSQIHLKATRAGG
Urocitellus_par   MVAAAVLLQCCPVLARGPTGLLSKVVKTHQFLFGTGRCPILATQGPICSQIHLKATRAGG
Sciurus_vulgari   MVAAAVLLQCCPVLARGPTGLLGKVVKTHQFLFGTGRCPILAAQGPICSQIHLKATKAGG
Sciurus_carolin   MVAAAVLLQCCPVLARGPTGLLGKVVKTHQFLFGTGRCPILATQGPICSQIHLKATKAGG
Sciurus_niger@A   MVAAAVLLQCCPVLVRGPTVLLGKVVKTHQFLFGTGRCPILATQGPICSQIHLKATKAGG
                  *****:**:.**** :*** **.** **:****. *******:*** *******:*.***

Alas2             ---------------DSPSWAKSHCPFMLSELQDRKSKIVQRAAPEVQEDVKTFKTDLL
Aplodontia_rufa   ---------------DSPSWAKGHCPFMLSELQDGKSKIVQKAAPEVQEDVKTFKTDLL
Xerus_inauris@A   ---------------DSPSWTKGHCPFMLSELQDGKSKIVQKAAPEVQEDVKTFKTDLL
Marmota_monax@A   GKKRFLEKGGCLGHSDDSPSWAKSHCPFMLSELQDRKSKIVQKAAPEVQEDVKTFKTDLL
Spermophilus_da   GKKRFLEKGGCLSHS-DSPSWAKSHCPFMLSELQDRKSKIVQKAAPEVQEDVKTFKTDLL
Ictidomys_tride   GKKRFLEKGGCLGHS-DSPSWAKSHCPFMLSELQDRKSKIVQKAAPEVQEDVKTFKTDLL
Urocitellus_par   GKKRFLEKGGCLGHS-DSPSWAKSHCPFMLSELQDRKSKIVQKAAPEVQEDVKTFKTDLL
Sciurus_vulgari   ---------------DSPSWSKGHCPFMLSELQDGKSKIVQKAAPEVQEDVKTFKTDLL
Sciurus_carolin   ---------------DSPSWSKGHCPFMLSELQDGKSKIVQKAAPEVQEDVKTFKTDLL
Sciurus_niger@A   ---------------DSPSWSKGHCPFMLSELQDGKSKIVQKAAPEVQEDVKTFKTDLL
                                 *****:*.*********** ******:*****************

Alas2             STMDSTTRSHSFPSFQEPEQTEGAVPHLIQNNMTGSQAFGYDQFFRDKIMEKKQDHTYRV
Aplodontia_rufa   STMDSTTRSHSFPSFQEPEQTEGAVPHLIQNNMTGEHAFGYDQFFRDKIMEKKQDHTYRV
Xerus_inauris@A   STMDSTTRSHSFPSFQEPEQTEGAVPHLIQNNMTGEHAFGYDQFFRDKIMEKKQDHTYRV
Marmota_monax@A   STMDSTTRSHSFPSFQEPEQTEGAVPHLIQNNMTGEHAFGYDQFFRDKIMEKKQDHTYRV
Spermophilus_da   STMDSTTRSHSFPSFQEPEQTEGAVPHLIQNNMTGEHAFGYDQFFRDKIMEKKQDHTYRV
Ictidomys_tride   STMDSTTRSHSFPSFQEPEQTEGAVPHLIQNNMTGEHAFGYDQFFRDKIMEKKQDHTYRV
Urocitellus_par   STMDSTTRSHSFPSFQEPEQTEGAVPHLIQNNMTGEHAFGYDQFFRDKIMEKKQDHTYRV
Sciurus_vulgari   STMDSTTRSHSFPSFQEPEQTEGAVPHLIQSNPAGEHAFGYDQFFRDKIMEKKQDHTYRV
Sciurus_carolin   STMDSTTRSHSFPSFQEPEQTEGAVPHLIQSNPAGEHAFGYDQFFRDKIMEKKQDHTYRV
Sciurus_niger@A   STMDSTTRSHSFPSFQEPEQTEGAVPHLIQSNPAGEHAFGYDQFFRDKIMEKKQDHTYRV
                  *****************************.* :*.:*******************

Alas2             FKTVNRWANAYPFAQHFSEASMASKDVSVWCSNDYLGISRHPRVLQAIEETLKNHGAGAG
Aplodontia_rufa   FKTVNRWANAYPFAQHFSEASMASKDVSVWCSNDYLGMSRHPRVLQAIQETLKNHGAGAG
Xerus_inauris@A   FKTVNRWANAYPFAQHFSEASMASKDVSVWCSNDYLGMSRHPRVLQAIQETLKNHGAGAG
Marmota_monax@A   FKTVNRWANAYPFAQHFSEASMASKDVSVWCSNDYLGISRHPRVLQAIEETLKNHGAGAG
Spermophilus_da   FKTVNRWANAYPFAQHFSEASMASKDVSVWCSNDYLGISRHPRVLQAIEETLKNHGAGAG
Ictidomys_tride   FKTVNRWANAYPFAQHFSEASMASKDVSVWCSNDYLGMSRHPRVLQAIQETLKNHGAGAG
Urocitellus_par   FKTVNRWANAYPFAQHFSEASMASKDVSVWCSNDYLGMSRHPRVLQAIQETLKNHGAGAG
Sciurus_vulgari   FKTVNRWANAYPFAQHFSEASMASKDVSVWCSNDYLGISRHPRVLQAIEETLKNHGAGAG
Sciurus_carolin   FKTVNRWANAYPFAQHFSEASMASKDVSVWCSNDYLGMSRHPRVLQAIQETLKNHGAGAG
Sciurus_niger@A   FKTVNRWANAYPFAQHFSEASMASKDVSVWCSNDYLGMSRHPRVLQAIQETLKNHGAGAG
                  *************************************:*********:***********

Alas2             GTRNISGTSKFHVELEQELAELHQKDSALLFSSCFVANDSTLFTLAKLLPGCEIYSDAGN
Aplodontia_rufa   GTRNISGTSKFHVELEQELAELHQKDSALLFSSCFVANDSTLFTLAKLLPGCEIYSDAGN
Xerus_inauris@A   GTRNISGTSKFHVELEQELAELHQKDSALLFSSCFVANDSTLFTLAKLLPGCEIYSDAGN
Marmota_monax@A   GTRNISGTSKFHVELEQELAELHQKDSALLFSSCFVANDSTLFTLAKLLPGCEIYSDAGN
Spermophilus_da   GTRNISGTSKFHVELEQELAELHQKDSALLFSSCFVANDSTLFTLAKLLPGCEIYSDAGN
Ictidomys_tride   GTRNISGTSKFHVELEQELAELHQKDSALLFSSCFVANDSTLFTLAKLLPGCEIYSDAGN
Urocitellus_par   GTRNISGTSKFHVELEQELAELHQKDSALLFSSCFVANDSTLFTLAKLLPGCEIYSDAGN
Sciurus_vulgari   GTRNISGTSKFHVELEQELAELHQKDSALLFSSCFVANDSTLFTLAKLLPGCEIYSDAGN
Sciurus_carolin   GTRNISGTSKFHVELEQELAELHQKDSALLFSSCFVANDSTLFTLAKLLPGCEIYSDAGN
Sciurus_niger@A   GTRNISGTSKFHVELERELAELHQKDSALLFSSCFVANDSTLFTLAKLLPGCEIYSDAGN
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Alas2              HASMIQGIRNSGAAKFVFRHNDPGHLKKLLEKSDPKTPKIVAFETVHSMDGAICPLEELC
Aplodontia_rufa    HASMIQGIRNSGAAKFVFRHNDPGHLKKLLEKSDPKTPKIVAFETVHSMDGAICPLEELC
Xerus_inauris@A    HASMIQGIRNSGAAKFVFRHNDPGHLKKLLEKSDPKTPKIVAFETVHSMDGAICPLEELC
Marmota_monax@A    HASMIQGIRNSGAAKFVFRHNDPGHLKKLLEKSDPKTPKIVAFETVHSMDGAICPLEELC
Spermophilus_da    HASMIQGIRNSGAAKFVFRHNDPGHLKKLLEKSDPKTPKIVAFETVHSMDGAICPLEELC
Ictidomys_tride    HASMIQGIRNSGAAKFVFRHNDPGHLKKLLEKSDPKTPKIVAFETVHSMDGAICPLEELC
Urocitellus_par    HASMIQGIRNSGAAKFVFRHNDPGHLKKLLEKSDPKTPKIVAFETVHSMDGAICPLEELC
Sciurus_vulgari    HASMIQGIRNSGAAKFVFRHNDPGHLKKLLEKSDPKTPKIVAFETVHSMDGAICPLEELC
Sciurus_carolin    HASMIQGIRNSGAAKFVFRHNDPGHLKKLLEKSDPKTPKIVAFETVHSMDGAICPLEELC
Sciurus_niger@A    HASMIQGIRNSGAAKFVFRHNDPGHLKKLLEKSDPKTPKIVAFETVHSMDGAICPLEELC
                   ************************************************************

Alas2              DVAHQYGALTFVDEVHAVGLYGARGAGIGERDGIMHKLDIISGTLGKAFGCVGGYIASTR
Aplodontia_rufa    DVAHQYGALTFVDEVHAVGLYGARGAGIGERDGIMHKLDIISGTLGKAFGCVGGYIASTR
Xerus_inauris@A    DVAHQYGALTFVDEVHAVGLYGARGAGIGERDGIMHKLDIISGTLGKAFGCVGGYIASTR
Marmota_monax@A    DVAHQYGALTFVDEVHAVGLYGARGAGIGERDGIMHKLDIISGTLGKAFGCVGGYIASTR
Spermophilus_da    DVAHQYGALTFVDEVHAVGLYGARGAGIGERDGIMHKLDIISGTLGKAFGCVGGYIASTR
Ictidomys_tride    DVAHQYGALTFVDEVHAVGLYGARGAGIGERDGIMHKLDIISGTLGKAFGCVGGYIASTR
Urocitellus_par    DVAHQYGALTFVDEVHAVGLYGARGAGIGERDGIMHKLDIISGTLGKAFGCVGGYIASTR
Sciurus_vulgari    DVAHQYGALTFVDEVHAVGLYGARGAGIGERDGIMHKLDIISGTLGKAFGCVGGYIASTR
Sciurus_carolin    DVAHQYGALTFVDEVHAVGLYGARGAGIGERDGIMHKLDIISGTLGKAFGCVGGYIASTR
Sciurus_niger@A    DVAHQYGALTFVDEVHAVGLYGARGAGIGERDGIMHKLDIISGTLGKAFGCVGGYIASTR
                   ************************************************************

Alas2              DLVDMVRSYAAGFIFTTSLPPMVLSGALESVRLLKGEEGQALRRAHQRNVKHMRQLLMDR
Aplodontia_rufa    DLVDMVRSYAAGFIFTTSLPPMVLSGALESVRLLKGEEGQALRRAHQRNVKHMRQLLMDR
Xerus_inauris@A    DLVDMVRSYAAGFIFTTSLPPMVLSGALESVRLLKGEEGQALRRAHQRNVKHMRQLLMDR
Marmota_monax@A    DLVDMVRSYAAGFIFTTSLPPMVLSGALESVRLLKGEEGQALRRAHQRNVKHMRQLLMDR
Spermophilus_da    DLVDMVRSYAAGFIFTTSLPPMVLSGALESVRLLKGEEGQALRRAHQRNVKHMRQLLMDR
Ictidomys_tride    DLVDMVRSYAAGFIFTTSLPPMVLSGALESVRLLKGEEGQALRRAHQRNVKHMRQLLMDR
Urocitellus_par    DLVDMVRSYAAGFIFTTSLPPMVLSGALESVRLLKGEEGQALRRAHQRNVKHMRQLLMDR
Sciurus_vulgari    DLVDMVRSYAAGFIFTTSLPPMVLSGALESVRLLKGEEGQALRRAHQRNVKHMRQLLMDR
Sciurus_carolin    DLVDMVRSYAAGFIFTTSLPPMVLSGALESVRLLKGEEGQALRRAHQRNVKHMRQLLMDR
Sciurus_niger@A    DLVDMVRSYAAGFIFTTSLPPMVLSGALESVRLLKGEEGQALRRAHQRNVKHMRQLLMDR
                   ************************************************************

Alas2              GFPVIPCPSHIIPIRVGNAALNSKICDLLLSKHSIYVQAINYPTVPRGEELLRLAPSPHH
Aplodontia_rufa    GLPVIPCPSHIIPIRVGNAALNSKICDLLLSKHSIYVQAINYPTVPRGEELLRLAPSPHH
Xerus_inauris@A    GLPVIPCPSHIIPIRVGDAALNSKICDLLLSKHSIYVQAINYPTVPRGEELLRLAPSPHH
Marmota_monax@A    GFPVIPCPSHIIPIRVGDAALNSKICDLLLSKHSIYVQAINYPTVPRGEELLRLAPSPHH
Spermophilus_da    GLPVIPCPSHIIPIRVGDAALNSKICDLLLSKHSIYVQAINYPTVPRGEELLRLAPSPHH
Ictidomys_tride    GFPVIPCPSHIIPIRVGDAALNSKICDLLLSKHSIYVQAINYPTVPRGEELLRLAPSPHH
Urocitellus_par    GLPVIPCPSHIIPIRVGDAALNSKICDLLLSKHSIYVQAINYPTVPRGEELLRLAPSPHH
Sciurus_vulgari    GLPVIPCPSHIIPIRVGDAALNSKICDLLLSKHSIYVQAINYPTVPRGEELLRLAPSPHH
Sciurus_carolin    GFPVIPCPSHIIPIRVGDAALNSKICDLLLSKHSIYVQAINYPTVPRGEELLRLAPSPHH
Sciurus_niger@A    GLPVIPCPSHIIPIRVGDAALNSKICDLLLSKHSIYVQAINYPTVPRGEELLRLAPSPHH
                   *:**************:*******************************************

Alas2              SPQMMENFVEKLL-----LAWTEVGLPLQDVSVAACNFCHRPVHFELMSEWERSYFGNMG
Aplodontia_rufa    SPQMMENFVEKLL-----LAWTEVGLPLQDVSVAACNFCHRPVHFELMSEWERSYFGNMG
Xerus_inauris@A    SPQMMENFVGKYLQSCGSFPGTCIKLSLQCLSL---------------------------
Marmota_monax@A    SPQMMENFVEKLL-----LAWTEVGLPLQDVSVAACNFCHRPVHFELMSEWERSYFGNMG
Spermophilus_da    SPQMMENFVEKLL-----LAWTEVGLPLQDVSVAACNFCHRPVHFELMSEWERSYFGNMG
Ictidomys_tride    SPQMMENFVEKLL-----LAWTEVGLPLQDVSVAACNFCHRPVHFELMSEWERSYFGNMG
Urocitellus_par    SPQMMENFVEKLL-----LAWTEVGLPLQDVSVAACNFCHRPVHFELMSEWERSYFGNMG
Sciurus_vulgari    SPQMMENFVEKLL-----VAWTEVGLPLQDVSVAACNFCHRPVHFELMSEWERSYFGNMG
```

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Sciurus_carolin   SPQMMENFVEKLL-----VAWTEVGLPLQDVSVAACNFCHRPVHFELMSEWERSYFGNMG
Sciurus_niger@A   SPQMMENFVEKLL-----VAWTEVGLPLQDVSVAACNFCHRPVHFELMSEWERSYFGNMG
                  ********* * *      .. * : *.** :*:


Alas2             PQYVTTYAZ
Aplodontia_rufa   PQYVTTYA-
Xerus_inauris@A   ---------
Marmota_monax@A   PQYVTTYA-
Spermophilus_da   PQYVTTYA-
Ictidomys_tride   PQYVTTYA-
Urocitellus_par   PQYVTTYA-
Sciurus_vulgari   PQYVTTYA-
Sciurus_carolin   PQYVTTYA-
Sciurus_niger@A   PQYVTTYA-
```

   CPOX encodes coproporphyrinogen oxidase. Diseases associated with *CPOX* include hereditary coproporphyria and harderoporphyria. Among its related pathways are porphyrin metabolism and biosynthesis of cofactors. Gene ontology (GO) annotations related to this gene include protein homodimerization activity and structural constituent of eye lens. An important paralog of this gene is *ENSG00000285635*. The protein encoded by this gene is the sixth enzyme of the heme biosynthetic pathway. The encoded enzyme is soluble and found in the intermembrane space of mitochondria. This enzyme catalyzes the stepwise oxidative decarboxylation of coproporphyrinogen III to protoporphyrinogen IX, a precursor of heme.

   Within a 426-amino acid *CPOX* sequence, we noted eight point-differences among sciurids. All members of *Sciurus* showed addition of a leucine at position 17. The human sequence had an insertion of two amino acids at positions 115-116.

```
Cpox              MALRLGRLGSDPWWRA-VLGDYAQLRAASPRCASARVCQLPGTAGPQPRRGLGYG-----
Aplodontia_rufa   MAWHLGRLSAGSCLRA-ARGGCGELRAWSQRCAGGRICRPPGTAGTESCRGLAHG-----
Xerus_inauris@C   MAWHLGRLSVGSCWRA-ARGGCGELRAWSQRCAAGRMCRPPGTTGTEHSRGLAQG-----
Marmota_monax@C   MAWYLGRLSAGPCWRA-ARGGCGELRAWSQRCATGRICQPPGTAGTMHSRGLAHG-----
Spermophilus_da   MAWYLGRLSAGPCWRA-ARGGCGELRAWSQRCATGRICQPPGTAGTGHSRGLLEGXXXXX
Ictidomys_tride   MAWYLGRLSAGPCWRA-ARGGCGELRAWSQRCATGHICQPPGTAGTVHSRGLAHG-----
Urocitellus_par   MAWYLGRLSAGPCWRA-ARGGCGELRAWSQRCATGRICQPPGTAGTVHSRGLAHG-----
Sciurus_vulgari   MAWHLGRLSAGPCWRALARGGCGELRAWSQRCAAGRICRPPGTAGTEHSRGLAHG-----
Sciurus_carolin   MAGHLGRLSAGPCWRALARGGCGELRAWSQRCAAGRICRPPGTAGTEHSRGLAHG-----
Sciurus_niger@C   MAWHLGRLSAGPCWRALARGGCGELRAWSQRCAAGRICRPPGTAGTEHSRGLAHG-----
                  **  ****. ..  ** . *. .:*** * *** .::*: ***:*.   ***  *


Cpox              -PWARGGSGLGTRLAATLAGLAGLAAAAFGHVQRAEMVPKSSGARSPSPGRREEDGDELA
Aplodontia_rufa   -PSARGSRWPGTGLTAALAGLAGLATAAVGHVHRAEMVPKSSGARSPSPERPLE--DELA
Xerus_inauris@C   -PSAKGGPWPGTGLAAALAGLAGLATAAFGHVQRAEMVPKSSGARSSSQERPLD--DDLA
Marmota_monax@C   -PSARGGPWPGTGLAAALAGLAGLATAAFGHVQRAEMVPKSSGARSPSPERPQE--DDLA
Spermophilus_da   XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXAEMVPKSSGARSPSPVRPQE--DDLA
Ictidomys_tride   -PSARGGPWPGTGLAAALAGLAGLATAAFGHVHRAEMVPKSSGARSPSPERPQE--DDLA
Urocitellus_par   -PSARGGPWPGTGLAAALAGLAGLATAAFGHVHRAEMVPKSSGARSPSPERPQE--DDLA
Sciurus_vulgari   -PSSGGGSWPGTGLATALAGLAGLATAAFGHVQRAEMVPKSSGARSPSPERSQE--DDLT
Sciurus_carolin   -PSSGGGSRPGAGLATALAGLAGLATAAFGHVQRAEMVPKSSGVRSPSPERPQE--DDLT
Sciurus_niger@C   -PSSGGGSRPGAGLATALAGLAGLATAAFGHVQRAEMVPKSSGVRSPSPERPQE--DDLT
                                              ********.**.*  *  :  *:*:


Cpox              RRCSTFMSSPVTELRELRRRPEDMKTKMELMIMETQAQVCRALAQVDGVADFTVDRWERK
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Aplodontia_rufa   RRCSCFMASPVTDLGELRRRPGDMKTKMELLILETQAQVCQALAQVDGGANFSVDRWERK
Xerus_inauris@C   RRCSCFMASPVTDLSELRKRPGDMKTKMELLILETQAQVCQALAQVDGGASFSVDRWERK
Marmota_monax@C   RRCSCFMASPVTDLDELRKRPGDMKTKMELLILETQAQVCQALAQVDGVASFSVDRWERK
Spermophilus_da   RRCSCFMASPVTDLDELRKRPGDMKTKMELLILETQAQVCQALAQVDGVASFSVDRWERK
Ictidomys_tride   RRCSCFMASPVTDLDELRKRPGDMKTKMELLILETQAQVCQALAQVDGVASFSVDRWERK
Urocitellus_par   RRCSCFMASPVTDLDELRKRPGDMKTKMELLILETQAQVCQALAQVDGVASFSVDRWERK
Sciurus_vulgari   RRCSCFMALPVTDLGELRKRPGDMKTKMELLILETQAQVCQALAQVDGGASFSVDRWERK
Sciurus_carolin   RRCSCFMALPVTDLGELRKRPGDMKTKMELLILETQAQVCQALAQVDGGASFSVDRWERK
Sciurus_niger@C   RRCSCFMALPVTDLGELRKRPGDMKTKMELLILETQAQVCQALAQVDGGASFSVDRWERK
                  **** **: ***:* ***:** ********:*:*******:******* *.*:*******


Cpox              EGGGGITCVLQDGRVFEKAGVSISVVHGNLSEEAANQMRGRGKTLKTKDSKLPFTAMGVS
Aplodontia_rufa   EGGGGISCVLQDGRVFEKAGVSISVVHGNLSEEAAKQMRSRGKILKTKDGKLPFTAMGVS
Xerus_inauris@C   EGGGGISCVLQDGRVFEKAGVSISVVHGNLSEEAAKQMRSRGKVLKTNDGKLPFSAMGVS
Marmota_monax@C   EGGGGISCVLQDGRVFEKAGVSISVVHGNLSEEAAKQMRSRGKVLKTKDGKLPFCAMGVS
Spermophilus_da   EGGGGISCVLQDGRVFEKAGVSISVVHGNLSEEAAKQMRSRGKVLKTKDGKLPFSAMGVS
Ictidomys_tride   EGGGGISCVLQDGRVFEKAGVSISVVHGNLSEEAAKQMRSRGKVLKTKDGKLPFSAMGVS
Urocitellus_par   EGGGGISCVLQDGRVFEKAGVSISVVHGNLSEEAAKQMRSRGKVLKTKDGKLPFSAMGVS
Sciurus_vulgari   EGGGGITCVLQDGRVFEKAGVSISVVHGNLSEEAAKQMRSRGKVLKTKDGKLPFSAMGVS
Sciurus_carolin   EGGGGISCVLQDGRVFEKAGVSISVVHGNLSEEAAKQMRSRGKVLKTKDGKLPFSAMGVS
Sciurus_niger@C   EGGGGISCVLQDGRVFEKAGVSISVVHGNLSEEAAKQMRSRGKVLKTKDGKLPFSAMGVS
                  ******:************************************:***.*** ***:*.**** *****


Cpox              SVIHPKNPYAPTMHFNYRYFEVEEADGNTHWWFGGGCDLTPTYLNQEDAVHFHRTLKEAC
Aplodontia_rufa   SVIHPKNPYAPTMHFNYRYFEVEEADGTKQWWFGGGCDLTPTYLNQEDAVHFHRTLKEAC
Xerus_inauris@C   SVIHPKNPHAPTIHFNYRYFEVEEADGTKQWWFGGGCDLTPTYLNQEDAVHFHRTLKEAC
Marmota_monax@C   SVIHPKNPHAPTIHFNYRYFEVEEADGTKQWWFGGGCDLTPTYLNQEDAVHFHRTLKEAC
Spermophilus_da   SVIHPKNPHAPTIHFNYRYFEVEEADGTKQWWFGGGCDLTPTYLNQEDAVHFHRTLKEAC
Ictidomys_tride   SVIHPKNPHAPTIHFNYRYFEVEEADGTKQWWFGGGCDLTPTYLNQEDAVHFHRTLKEAC
Urocitellus_par   SVIHPKNPHAPTIHFNYRYFEVEEADGTKQWWFGGGCDLTPTYLNQEDAVHFHRTLKEAC
Sciurus_vulgari   SVIHPKNPYAPTMHFNYRYFEVEEADGNTQWWFGGGCDLTPTYLNQEDAVHFHRTLKEAC
Sciurus_carolin   SVIHPKNPYAPTIHFNYRYFEVEEADGNKQWWFGGGCDLTPTYLNQEDAVHFHRTLKEAC
Sciurus_niger@C   SVIHPKNPYAPTIHFNYRYFEVEEADGNKQWWFGGGCDLTPTYLNQEDAVHFHRTLKEAC
                  ********:***:**************..:*****************************


Cpox              DQHGPDIYPKFKKWCDDYFFIVHRGERRGIGGIFFDDLDSPSKEEAFRFVKTCAEAVVPS
Aplodontia_rufa   DQHGPDLYPKFKKWCDDYFFIVHRGERRGIGGIFFDDLDSPSKEEVFRFVKSCAQAVVPS
Xerus_inauris@C   DQHGPDLYPKFKKWCDDYFFITHRGERRGIGGIFFDDLDSPSKEEVFHFVQSCARAVVPS
Marmota_monax@C   DQHGPDLYPKFKKWCDDYFFIAHRGERRGIGGIFFDDLDSPSKEEVFRFVQSCAQAVVPS
Spermophilus_da   DQHGPDLYPKFKKWCDDYFFIAHRGERRGIGGIFFDDLDSPSKEEVFRFVQSCAQAVVPS
Ictidomys_tride   DQHGPDLYPKFKKWCDDYFFIAHRGERRGIGGIFFDDLDSPSKEEVFRFVQSCAQAVVPS
Urocitellus_par   DQHGPDLYPKFKKWCDDYFFIAHRGERRGIGGIFFDDLDSPSKEEVFRFVQSCAQAVVPS
Sciurus_vulgari   DQHGPDLYPKFKKWCDDYFFITHRGERRGIGGIFFDDLDSPSKEEAFRFVKTCAEAVVPS
Sciurus_carolin   DQHGPDIYPKFKKWCDDYFFITHRGERRGIGGIFFDDLDSPSKEEAFRFVKTCAEAVVPS
Sciurus_niger@C   DQHGPDLYPKFKKWCDDYFFITHRGERRGIGGIFFDDLDSPSKEEAFRFVKTCAEAVVPS
                  ******:*************.*********************.*:**::**.*****


Cpox              YVPIVKKHCDDSYTPRDKLWQQLRRGRYVEFNLLYDRGTKFGLFTPGSRIESILMSLPLT
Aplodontia_rufa   YIPLVKKHCDDSFTPQEKLWQQLRRGRYVEFNLLYDRGTKFGLFTPGSRIESILMSLPLT
Xerus_inauris@C   YIPLVKKHCDDSFTPQEKLWQQLRRGRYVEFNLLYDRGTKFGLFTPGSRIESILMSLPLT
Marmota_monax@C   YIPLVKKHCDDSFTPQEKLWQQLRRGRYVEFNLLYDRGTKFGLFTPGSRIESILMSLPLT
Spermophilus_da   YIPLVKKHCDDSYTPREKLWQQLRRGRYVEFNLLYDRGTKFGLFTPGSRIESILMSLPLT
Ictidomys_tride   YIPLVKKHCDDSFTPQEKLWQQLRRGRYVEFNLLYDRGTKFGLFTPGSRIESILMSLPLT
Urocitellus_par   YIPLVKKHCDDSFTPQEKLWQQLRRGRYVEFNLLYDRGTKFGLFTPGSRIESILMSLPLT
Sciurus_vulgari   YVPIVKKHCDDSYTPRDKLWQQLRRGRYVEFNLLYDRGTKFGLFTPGSRIESILMSLPLT
Sciurus_carolin   YVPLVKKHCDDSYTPQEKLWQQLRRGRYVEFNLLYDRGTKFGLFTPGSRIESILMSLPLT
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Sciurus_niger@C  YVPLVKKHCDDSYTPQEKLWQQLRRGRYVEFNLLYDRGTKFGLFTPGSRIESILMSLPLT
                 *:*:********:**:******************************************

Cpox             ARWEYMHSPPENSKEAEILEVLRHPKDWVHZ
Aplodontia_rufa  AR----------------------------
Xerus_inauris@C  AR----------------------------
Marmota_monax@C  AR----------------------------
Spermophilus_da  AR----------------------------
Ictidomys_tride  AR----------------------------
Urocitellus_par  AR----------------------------
Sciurus_vulgari  ARWEYMHSPPENSKAKT--QSLHPPRDWVH-
Sciurus_carolin  ARWAYMHLPPENSKEAEILRVLHHPRDWVH-
Sciurus_niger@C  ARWAYMHSPPENSK----------------
                 **
```

FECH encodes ferrochelatase. Diseases associated with *FECH* include erythropoietic protoporphyria 1 and autosomal erythropoietic protoporphyria. Among its related pathways are porphyrin metabolism and the HIF-1-alpha transcription factor network. Gene ontology (GO) annotations related to this gene include iron ion binding and 2 iron, 2 sulfur cluster binding. The protein encoded by this gene is localized to the mitochondrion, where it catalyzes the insertion of the ferrous form of iron into protoporphyrin IX in the heme synthesis pathway. Two transcript variants encoding different isoforms have been found for this gene.

Among 319 amino acids for FECH, sciurids differed at three. *X. inauris* had a 10-amino acid deletion at positions 256-265, and M. monax a 15-amino acid deletion at positions 250-264.

```
Fech             MLSASANMAAALRAAGALLREPLVHGSSRACQPWRCQ-SGAAVAATTEKVHHAKTTKPQA
Aplodontia_rufa  ------------------------------------------------------------
Xerus_inauris@F  --------------------LVCGNLRASRSWKCKLNTIAVAVDKGKDQCVKNANPQV
Marmota_monax@F  --------------------LVLGNSKASQSWKCKLNTTAVAVHTGKVQFVKNKNPQV
Spermophilus_da  --------------------LVLGNSKASQSWKCKLNTTAVAVHTGKVQFVKNKNLQV
Ictidomys_tride  ------------------------------------------------------------
Urocitellus_par  --------------------LVLGNSKASQSWKCKLNTTAVAVHTGKVQFVKNKNPQV
Sciurus_vulgari  ------------------------------------------------------------
Sciurus_carolin  ------------------------------------------------------------
Sciurus_niger@F  ------------------------------------------------------------


Fech             QPERRKPKTGILMLNMGGPETLGEVQDFLQRLFLDRDLMTLPIQNKLAPFIAKRRTPKIQ
Aplodontia_rufa  -------------------------------------------SKLAPFIAKRRTPKIQ
Xerus_inauris@F  QLEKKKPKTGI-MLNIGGPETLGEVQDFLQRLFLDRDLIIFPI-NKLAPFIAKRRTPKIQ
Marmota_monax@F  QLEKKNPKTGILMLNIGGPETLGEVQDFLQRLFLDRDLMIFPI-NKLAPFIAKRRTPKIQ
Spermophilus_da  QLE-KNPKTGILMLNIGGPETLGEVQDFLQRLFLDRDLMIFPI-NKLAPFIAKRRTPKIQ
Ictidomys_tride  -------------------------------------------SKLAPFIAKRRTPKIQ
Urocitellus_par  QLEKKNPKTGILMLNIGGPETLGEVQDFLQRLFLDRDLMIFPI-NKLAPFIAKRRTPKIQ
Sciurus_vulgari  -------------------------------------------SKLAPFIAKRRTPRIQ
Sciurus_carolin  -------------------------------------------SKLAPFIAKRRTPRIQ
Sciurus_niger@F  -------------------------------------------SKLAPFIAKRRTPRIQ
                                                            .***********:**


Fech             EQYRRIGGGSPIKMWTSKQGEGMVKLLDELSPATAPHKYYIGFRYVHPLTEEAIEEMERD
Aplodontia_rufa  EQYRRIGGGSPIKMWTSKQGEGMVKLLDDLSPDTAPHKYYIGFRYVHPLTEEAIDKMERD
Xerus_inauris@F  EQYRRIGGGSPIKMWTSKQGEGMVKLLDELSPATAPHKYYIGFRYVHPLTEEAIEEMERD
Marmota_monax@F  EQYRRIGGGSPIKMWTSKQGEGMVKLLDELSPATAPHKYYIGFRYVHPLTEEAIEEMERD
Spermophilus_da  EQYRRIGGGSPIKMWTSKQGEGMVKLLDELSPATAPHKYYIGFRYVHPLTEEAIEEMERD
```

```
Ictidomys_tride   EQYRRIGGGSPIKMWTSKQGEGMVKLLDELSPNTAPHKYYIGFRYVHPLTEEAIEEMERD
Urocitellus_par   EQYRRIGGGSPIKMWTSKQGEGMVKLLDELSPATAPHKYYIGFRYVHPLTEEAIEEMERD
Sciurus_vulgari   EQYRRIGGGSPIKMWTSKQGEGMVKLLDELSPTTAPHKYYIGFRYVHPLTEEAIDEMERD
Sciurus_carolin   EQYRRIGGGSPIKMWTSKQGEGMVKLLDELSPTTAPHKYYIGFRYVHPLTEEAIDEMERD
Sciurus_niger@F   EQYRRIGGGSPIKMWTSKQGEGMVKLLDELSPTTAPHKYYIGFRYVHPLTEEAIDEMERD
                  *****************************:*** ********************::****


Fech              GLERAIAFTQYPQYSCSTTGSSLNAIYRYYNEVGQKPTMKWSTIDRWPTHPLLIQCFADH
Aplodontia_rufa   GLERAIAFTQYPQYSCSTTGSSLNAIYRYYNEVGKKPTMKWSTIDRWPTHPLLIQVSQDH
Xerus_inauris@F   GLERAIAFTQYPQYSCSTTGSSLNAIYRYYNEVGQKPTMKWSTIDRWPTHPLLIQCFADN
Marmota_monax@F   GLERAIAFTQYPQYSCSTTGSSLNAIYRYYNEVGQKPTMKWSTIDRWPTHPLLIQCFADY
Spermophilus_da   GLERAIAFTQYPQYSCSTTGSSLNAIYRYYNEVGQKPTMKWSTIDRWPTHPLLIQCFADH
Ictidomys_tride   GLERAIAFTQYPQYSCSTTGSSLNAIYRYYNEVGQKPTMKWSTIDRWPTHPLLIQCFADH
Urocitellus_par   GLERAIAFTQYPQYSCSTTGSSLNAIYRYYNEVGQKPTMKWSTIDRWPTHPLLIQCFADH
Sciurus_vulgari   GLERAIAFTQYPQYSCSTTGSSLNAIYRYYNEVGKKPTMKWSTIDRWPTHPLLIQVSQDH
Sciurus_carolin   GLERAIAFTQYPQYSCSTTGSSLNAIYRYYNEVGKKPTMKWSTIDRWPTHPLLIQVSQDH
Sciurus_niger@F   GLERAIAFTQYPQYSCSTTGSSLNAIYRYYNEVGKKPTMKWSTIDRWPTHPLLIQVSQDH
                  **********************************:******************    *


Fech              ILKELNHFPEEKRSEVVILFSAHSLPMSVVNRGDPYPQEVGATVHKVMEKLGYPNPYRLV
Aplodontia_rufa   ILKELNHFPEEKRSEVVILFSAHSLPLQVVNRGDPYPQEVGATVHKVMESLGYSNPYRLV
Xerus_inauris@F   LQKELHHFPLEKGGH----------QMSVVNRGDPYPQEVGATVHKVMEKLGYPNPYRLV
Marmota_monax@F   LQKELHHFP--------------LPMSVVNRGDPYPQEVGATVHKVMERLGYSNPYRLV
Spermophilus_da   ILKELNHFPEEKRSEVVILFSAHSLPMSVVNRGDPYPQEVGATVHKVMERLGYSNPYRLV
Ictidomys_tride   ILKELNHFPEEKRSEVVILFSAHSLPMSVVNRGDPYPQEVGATVHKVMERLGYSNPYRLV
Urocitellus_par   ILKELNHFPEEKRSEVVILFSAHSLPMSVVNRGDPYPQEVGATVHKVMERLGYSNPYRLV
Sciurus_vulgari   ILKELNHFPEEKRSEVVILFSAHSLPMQVVNRGDPYPQEVGATVHKVMERLGYSNPYRLV
Sciurus_carolin   ILKELNHFPEEKRSEVVILFSAHSLPMQVVNRGDPYPQEVGATVHKVMERLGYSNPYRLV
Sciurus_niger@F   ILKELNHFPEEKRSEVVILFSAHSLPMQVVNRGDPYPQEVGATVHKVMERLGYSNPYRLV
                  : ***:***                  :.******************* ***.******


Fech              WQSKVGPVPWLGPQTDEAIKGLCERGRKNILLVPIAFTSDHIETLYELDIEYSQVLAQKC
Aplodontia_rufa   WQSKVGPVSWLGPQTDEAIKGLCERGRKNILLVPIAFTSDHIETLYELDIEYSQILAKEC
Xerus_inauris@F   WQSKVGPVPWLGPQTDEAIKGLCERGRKNILLVPIAFTSDHIETLYELDIEYSQVLAQKC
Marmota_monax@F   WQSKVGPVPWLGPQTDEAIKGLCERGRKNILLVPIAFTSDHIETLYELDIEYSQVLAQKY
Spermophilus_da   WQSKVGPVPWLGPQTDEAIKGLCERGRKNILLVPIAFTSDHIETLYELDIEYSQVLAKEV
Ictidomys_tride   WQSKVGPVPWLGPQTDEAIKGLCERGRKNILLVPIAFTSDHIETLYELDIEYSQVLAKEV
Urocitellus_par   WQSKVGPVPWLGPQTDEAIKGLCERGRKNILLVPIAFTSDHIETLYELDIEYSQVLAKEC
Sciurus_vulgari   WQSKVGPVPWLGPQTNEAIKGLCERGRKNILLVPIAFTSDHIETLYELDIEYSQVLAKEV
Sciurus_carolin   WQSKVGPVPWLGPQTNEAIKGLCERGRKNILLVPIAFTSDHIETLYELDIEYSQVLAKEC
Sciurus_niger@F   WQSKVGPVPWLGPQTNEAIKGLCERGRKNILLVPIAFTSDHIETLYELDIEYSQVLAKEC
                  ********.******:*********************************************:**::


Fech              GAENIRRAESLNGNPLFSKALADLVHSHIQSNKLCSTQLSLNCPLCVNPVCRKTKSFFTS
Aplodontia_rufa   GAENIRRAESLNGNPLFSQALADLVHSHIQSNRLCSKQLTLSCPLCVNPVCRETKSFFTN
Xerus_inauris@F   GAENIMKRESFAGNPLFSQALADLVYSHIQSNKLCSKQLTLSCPLCVNPVCRETKSFFTN
Marmota_monax@F   -VENNKRGESLNGNPLFSQALADLVLSHIQSNKLCSKQLTLSCPLCVNPVCRETKSFFTN
Spermophilus_da   GAENIRRAESLNGNPLFSQALADLVLSHIQSNKLCSKQLTLSCPLCVNPVCRETKSFFTN
Ictidomys_tride   GAENIRRAESLNGNPLFSQALADLVLSHIQSNKLCSKQLTLSCPLCVNPVCRETKSFFTN
Urocitellus_par   GAENIRRAESLNGNPLFSQALADLVLSHIQSNKLCSKQLTLSCPLCVNPVCRETKSFFTN
Sciurus_vulgari   STENIRRAESLNGNPLFSQALADLVHSHIQSNTQCSKQLTLSCPLCVNPVCRETKSFFTN
Sciurus_carolin   GAENIRRAESLNGNPLFSQALADLVHSHIQSNTLCSKQLTLSCPLCVNPVCRETKSFFTN
Sciurus_niger@F   GAENIRRAESLNGNPLFSQALADLVHSHIQSNTLCSKQLTLSCPLCVNPVCRETKSFFTN
                  .**   : **: ******:****** ******  **.**:*.***********:******.


Fech              QQLZ
```

```
Aplodontia_rufa QQL-
Xerus_inauris@F QQL-
Marmota_monax@F QQL-
Spermophilus_da QQL-
Ictidomys_tride QQL-
Urocitellus_par QQL-
Sciurus_vulgari QQM-
Sciurus_carolin QQM-
Sciurus_niger@F QQM-
                **:
```

HMBS encodes hydroxymethylbilane synthase. Diseases associated with *HMBS* include acute intermittent porphyria and mood disorder. Among its related pathways are porphyrin metabolism and biosynthesis of cofactors. Gene ontology (GO) annotations related to this gene include hydroxymethylbilane synthase activity. The encoded protein is the third enzyme of the heme biosynthetic pathway and catalyzes the head-to-tail condensation of four porphobilinogen molecules into the linear hydroxymethylbilane. Alternatively spliced transcript variants encoding different isoforms have been described.

Among 242 amino acids in *Sciurus niger* HMBS, there were two point-differences among *Sciurus* species and an insertion of 37 amino acids in *S. vulgaris*. There were major amino acid sequence insertions among all species, including 37 amino acids in *A. rufa*; five amino acids for *M. monax, I. dauricus*, and *U. parryi*; and eight amino acids for *S. dauricus*.

```
Hmbs             MSGNGGAATTAEENGSKMRVIRVGTRKSQLARIQTDTVVAMLKALYPGIQFEIIAMSTTG
Aplodontia_rufa  ------------------------------------------------------------
Xerus_inauris@H  ------------------------------------------------------------
Marmota_monax@H  ------------------------------------------------------------
Spermophilus_da  ------------------------------------------------------------
Ictidomys_tride  ------------------------------------------------------------
Urocitellus_par  ------------------------------------------------------------
Sciurus_vulgari  ------------------------------------------------------------
Sciurus_carolin  ------------------------------------------------------------
Sciurus_niger@H  ------------------------------------------------------------


Hmbs             DKILDTALSKIGEKSLFTKELENALEKNEVDLVVHSLKDVPTILPPGFTIGAICKRENPC
Aplodontia_rufa  ----------------------------------------ICPSFHDLPSFPRRENPY
Xerus_inauris@H  --------------------------------------------------RRENPC
Marmota_monax@H  --------------------------------------------------RRENPC
Spermophilus_da  --------------------------------------------------RRENPC
Ictidomys_tride  --------------------------------------------------RRENPC
Urocitellus_par  --------------------------------------------------RRENPC
Sciurus_vulgari  ------------------------------------------------------
Sciurus_carolin  --------------------------------------------------RRENPC
Sciurus_niger@H  --------------------------------------------------RRENPC


Hmbs             DAVVFHPKFIGKTLETLPEK-----------------------------------SAV
Aplodontia_rufa  DAVVFHPKFVGKTLETLPEKRVGPEWAAWWDVHRRWKAGRSRKGTVTICISFTFSLSSTV
Xerus_inauris@H  DAVVFHPKFVGKTLETLPEK-----------------------------------SAV
Marmota_monax@H  DAVVFHPKFVGKTLETLPEK-----------------------------------SAV
Spermophilus_da  DAVVFHPKFVGKTLETLPEK-----------------------------------SAV
```

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Ictidomys_tride DAVVFHPKFVGKTLETLPEK------------------------------------SAV
Urocitellus_par DAVVFHPKFVGKTLETLPEK------------------------------------SAV
Sciurus_vulgari ------------------------------------------------------------
Sciurus_carolin DAVVFHPKFVGKTLETLPEK------------------------------------SAV
Sciurus_niger@H DAVVFHPKFVGKTLETLPEK------------------------------------SAV


Hmbs            GTSSLRRVAQLQRKFPHLEFKSI-----RGNLNTRLRKLDELQEFSAIVLAVAGLQRMGW
Aplodontia_rufa GTSSLRRAAQLQRKFPHLEFKNI-----RGNLNTRLRKLDEQHEFSAIILAVAGLQRMGW
Xerus_inauris@H GTSSLRRAAQLQRKFPHLEFKSI-----RGNLNTRLRKLDEQHEFSAIILAVAGLQRMGW
Marmota_monax@H GTSSLRRAAQLQRKFPHLEFKSIVSFRRRGNLNTRLRKLDEQHEFSAIILAVAGLQRMGW
Spermophilus_da GTSSLRRAAQLQRKFPHLEFKSIVSFRRRGNLNTRLRKLDEQHEFSAIILAVAGLQRMGW
Ictidomys_tride GTSSLRRAAQLQRKFPHLEFKSI-----RGNLNTRLRKLDEQHEFSAIILAVAGLQRMGW
Urocitellus_par GTSSLRRAAQLQRKFPHLEFKSIVSFRRRGNLNTRLRKLDEQHEFSAIILAVAGLQRMGW
Sciurus_vulgari --------------------------RGNLNTRLRKLDEQHEFSAIILAVAGLQRMGW
Sciurus_carolin GTSSLRRAAQLQRKFPHLEFKSI-----RGNLNTRLRKLDEQHEFSAIILAVAGLQRMGW
Sciurus_niger@H GTSSLRRAAQLQRKFPHLEFKSI-----RGNLNTRLRKLDEQHEFSAITLAVAGLQRMGW
                                            ************* :***** **********


Hmbs            QNRVGQI-----------LHPEECMYAVGQGALAVEVRAKDQDILDLVSVLHDPETLLRC
Aplodontia_rufa QNRVGQVGASPLPSPIYLLLPPPCFFSVGQGALGVEVRAKDQDILDLVGVLHDPETLLRC
Xerus_inauris@H QNRVGQV-----------GAPNECMYAVGQGALGVEVRAKDQDILDLVGVLHDPETLLRC
Marmota_monax@H QNRVGQV-----------LHPEECMYAVGQGALAVEVRAKDQDILDLVGVLHDPETLLRC
Spermophilus_da QNRVGQV-----------LHPEECMYAVGQGALAVEVRAKDQDILDLVGVLHDPETLLRC
Ictidomys_tride QNRVGQI-----------VERRSSLMCFHQGALAVEVRAKDQDILDLVGVLHDPETLLRC
Urocitellus_par QNRVGQI-----------LERRSSLMCFHQGALAVEVRAKDQDILDLVGVLHDPETLLRC
Sciurus_vulgari QNRVGQV-----------LHPEECMYAVGQGALGVEVRAKDQDILDLVGVLHDPETLLRC
Sciurus_carolin QNRVGQV-----------LHPEECMYAVGQGALGVEVRAKDQDILDLVGVLHDPETLLRC
Sciurus_niger@H QNRVGQV-----------LHPEECMYAVGQGALGVEVRAKDQDILDLVGVLHDPETLLRC
                ******:              .: .. ****.************** .***********


Hmbs            IAERAFLRHL--------EGGCSVPVAVHTVMKDG----------------------
Aplodontia_rufa IAERAFLRHL--------EGGCSVPVAVHTVMKDG----------------------
Xerus_inauris@H IAERAFLRHL--------EGGCSVPVAVHTVMKDG----------------------
Marmota_monax@H IAERAFLRHL--------EGGCSVPVAVHTVIKDG----------------------
Spermophilus_da IAERAFLRHL--------EGGCSVPVAVHTVIKDG----------------------
Ictidomys_tride IAERAFLRHLVGPVLVLEEGGCSVPVAVHTVIKDG----------------------
Urocitellus_par IAERAFLRHL--------EGGCSVPVAVHTVIKDG----------------------
Sciurus_vulgari IAERAFLRHL--------EGGCSVPVAVHTVMKDGQVSSGKWAGRQRTGISPYASQVSKQ
Sciurus_carolin IAERAFLRHL--------VGGCSVPVAVHTVMKDG----------------------
Sciurus_niger@H IAERAFLRHL--------VGGCSVPVAVHTVMKDG----------------------
                **********        ************:***


Hmbs            -----------QLYLTGGVWSLDGSDSMQETMQATIQVPVQQEDGPEDDPQLVGITARN
Aplodontia_rufa -----------QLYLTGGVWSLDGSDSMQETMQATIHVPVQHEDGPEDDPQLVGITARN
Xerus_inauris@H -----------QLYLTGGVWSLDGSDSMQETMQATINVPVQYEDGPEDDPQLVGITARN
Marmota_monax@H -----------QLYLTGGVWSLDGSDSMQETMQATIHVPVQDHGPEDDPQLVGITARN
Spermophilus_da -----------QLYLTGGVWSLDGSDSMQETMQATIHVPVQYDDGPEDDPQLVGITALN
Ictidomys_tride -----------QLYLTGGVWSLDGSDSMQETMQATIHVPTQQYDGPEDDPQLVGITALN
Urocitellus_par -----------QLYLTGGVWSLDGSESMQETMQATIHVPVQYDNGPEDDPQLVGITALN
Sciurus_vulgari SPLRICNNYFLSQLYLTGGVWSLDGSDSMQETMQATIHVPVQYEDGPEDDPQLVGITARN
Sciurus_carolin -----------QLYLTGGVWSLDGSDSMQETMQATIQVPIQYEDGPEDDPQLVGITARN
Sciurus_niger@H -----------QLYLTGGVWSLDGSDSMQETMQATIQVPIQYEDGPEDDPQLVGITARN
                            **************:**********:** *   .************ *


Hmbs            IPRGAQLAAENLGISLASLLLNKGAKNILDVARQLNDVRZ
```

```
Aplodontia_rufa  IPRGAQLAAENLGISLANLLLNKGAKNILDVARQLNDVH-
Xerus_inauris@H  IPRGAQLAAENLGISLANLLLNKGAKNILDVARQLNDV--
Marmota_monax@H  IPRGAQLAAENLGISLASLLLNKGAKNILDVARQLNDVH-
Spermophilus_da  IPRGAQLAAENLGISLASLLLNKGAKNILDVARQLNDVH-
Ictidomys_tride  IPRGAQLAAENLGISLASLLLNKGAKNILDVARQLNDVH-
Urocitellus_par  IPRGAQLAAENLGISLASLLLNKGAKNILDVARQVNDVH-
Sciurus_vulgari  IPRGAQLAAENLGISLANLLLNKGAKNILDVARQLNDV--
Sciurus_carolin  IPRGAQLAAENLGISLANLLLNKGAKSILDVARQLNDV--
Sciurus_niger@H  IPRGAQLAAENLGISLANLLLNKGAKSILDVARQLNDV--
                 *****************.********.*******:***
```

PPOX encodes protoporphyrinogen oxidase. Among its related pathways are porphyrin and biosynthesis of cofactors. Gene ontology (GO) annotations related to this gene include oxidoreductase activity and oxygen-dependent protoporphyrinogen oxidase activity. This gene encodes the penultimate enzyme of heme biosynthesis, which catalyzes the 6-electron oxidation of protoporphyrinogen IX to form protoporphyrin IX. Mutations in this gene cause variegate porphyria, an autosomal dominant disorder of heme metabolism resulting from a deficiency in protoporphyrinogen oxidase, an enzyme located on the inner mitochondrial membrane. Alternatively spliced transcript variants encoding the same protein have been identified.

Relative to a 557-amino acid sequence for *S. niger*, we observed four point-differences among sciurids. There were insertions of 31 amino acids for *M. monax* and *X. inauris*, 25 for *S. niger*, 24 for *M. monax* and *I. tridecemlineatus,* and 25 for *X. inauris*. There was a deletion of 32 amino acids for *A. rufa;* of 35 for *A. rufa*, *X. inauris*, and *I. tridecemlineatus*; of eight amino acids in *A. rufa*, *X. inauris*, and *I. tridecemlineatus*; and of 26 amino acids for *M. monax* and *S. dauricus*.

```
Ppox             MGRTVIVLGGGISGLAASYHLIRGPSPPKVILVEGSKRLGGWIRSIRGSDGAIFELGPRG
Aplodontia_rufa  ----------------------SPPCRQVVLVEGSKRLGGWIRSVRGPDGAIFELGPRG
Xerus_inauris@P  -----------------------PSCRQVVLVEGSKRLGGWIRSVRGPDGAIFELGPRG
Marmota_monax@P  --------------------------QVVLVEGSKRLGGWIRSIRGPGGAIFELGPRG
Spermophilus_da  --------------------------QVVLVEGSKRLGGWIRSIRGPGGAIFELGPRG
Ictidomys_tride  --------------------------QVVLVEGSKRLGGWIRSIRGPGGAIFELGPRG
Urocitellus_par  --------------------------QVVLVEGSKRLGGWIRSIRGPGGAIFELGPRG
Sciurus_vulgari  -----------------------PSCRQVVLVEGSKRLGGWIRSVRGPDGAIFELGPRG
Sciurus_carolin  ---------------AASDGTTMAPSCRQVVLVEGSKRLGGWIRSVRGPDGAIFELGPRG
Sciurus_niger@P  -----------------------PSCRQVVLVEGSKRLGGWIRSVRGPDGAIFELGPRG
                                         :*:**************:**..*********
```

```
Ppox             IRPAGALGARTLLLVSELGLESEVLPVRGDHPAAQNRFLYVGGTLHPLPSGLRGLLRPSP
Aplodontia_rufa  IRPAGALGARTLLLVSELGLESEVLPVRGDHPAAQNRFLYVGGTLHPLPSGLRGLLRPSP
Xerus_inauris@P  IRPAGPLGARTLLLVSELGLESEVLPVRGDHPAAQNRFLYVGGTLHPLPSGLRGLLRPSP
Marmota_monax@P  IRPAGVLGARTLLLVSELGLESEVLPVRGDHPAAQNRFLYVGGTLHPLPSGLRGLLRPSP
Spermophilus_da  IRPAGVLGARTLLLVSELGLESEVLPVRGDHPAAQNRFLYVGGTLHPLPSGLRGLLRPSP
Ictidomys_tride  IRPAGVLGARTLLLVSELGLESEVLPVRGDHPAAQNRFLYVGGTLHPLPSGLRGLLRPSP
Urocitellus_par  IRPAGVLGARTLLLVSELGLESEVLPVRGDHPAAQNRFLYVGGTLHPLPSGLRGLLRPSP
Sciurus_vulgari  IRPAGALGARTLLLVSELGLESEVLPVRGDHPAAQNRFLYVGGTLHPLPSGLRGLLRPSP
Sciurus_carolin  IRPAGALGARTLLLVSELGLESEVLPVRGDHPAAQNRFLYVGGTLHPLPSGLRGLLRPSP
Sciurus_niger@P  IRPAGALGARTLLLVSELGLESEVLPVRGDHPAAQNRFLYVGGTLHPLPSGLRGLLRPSP
                 *****  *****************************************************
```

```
Ppox             PFSKPLFWAGLRELLKPRGKEPDETVHSFAQRRLGPEVASLAMDSLCRGVFAGNSRELSI
Aplodontia_rufa  PFSKSLLWTGLRELTKPRGKEPDETVHSFAQRRLGPEVASLVMDSLCRGVFAGNSRELSV
```

```
Xerus_inauris@P    PFSKPLLWAGLRELTKPRGKEPDETVHSFAQRRLGPEVASLAMDSLCRGVFAGNSRELSI
Marmota_monax@P    PFSKPLLWAGLRELTKPRGKEPDETVHSFAQRRLGPEVASLAMDSICRGVFAGNSRELSI
Spermophilus_da    PFSKPLLWAGLRELTKPRGKEPDETVHSFAQRRLGPEVASLAMDSLCRGVFAGNSRELSI
Ictidomys_tride    PFSKPLLWAGLRELTKPRGKEPDETVHSFAHRRLGPEVASLVMDSLCRGVFAGNSRELSI
Urocitellus_par    PFSKPLLWAGLRELTKPRGKEPDETVHSFAQRRLGPEVASLVMDSLCRGVFAGNSRELSI
Sciurus_vulgari    PFSRPLLWAGLRELTKPRSKEPDETVHSFAQRRLGPEVASLAMDSLCRGVFAGNSRELSI
Sciurus_carolin    PFSRPLLWAGLRELTKPRSKEPDETVHSFAQRRLGPEVASLAMDSLCRGVFAGNSRELSI
Sciurus_niger@P    PFSRPLLWAGLRELTKPRSKEPDETVHSFAQRRLGPEVASLAMDSLCRGVFAGNSRELSI
                   ***:.*:*:***** ***.***********:********** .***:************* :


Ppox               RSCFPSLFQAEQTHRSILLGLLLG-----------------------------AGQSP
Aplodontia_rufa    RSCFPSLFQAEQTHRSILLGLLLG-----------------------------AGQSP
Xerus_inauris@P    RSCFPSLFQAEQTYRSIILGLLLGAGEEGLVQRVKILRTARVRQGVLVRFFFAVSLGQSP
Marmota_monax@P    RSCFPSLFQAEQTHRSVILGLLFS-----------------------------SGQSP
Spermophilus_da    RSCFPSLFQAEQTHRSVILGLLFS-----------------------------SGKSP
Ictidomys_tride    RSCFPSLFQAEQTHRSVILGLLFS-----------------------------SGKSP
Urocitellus_par    RSCFPSLFQAEQTHRSVILGLLFS-----------------------------SGKSP
Sciurus_vulgari    RSCFPSLFQAEQTHRSIILGLLLG-----------------------------AGQSP
Sciurus_carolin    RSCFPSLFQAEQTHRSIILGLLLG-----------------------------AGQSP
Sciurus_niger@P    RSCFPSLFQAEQTHRSIILGLLLGAGE------VAGRYGLPVRQGVLIFFFAAASAGQSP
                   *************:**::****:.                              *:**


Ppox               QPDSSLIRQARAERWSQWSLRGGLEVLPQALHNHLASKGVTVLSGQPVCGLSLQPEGRWK
Aplodontia_rufa    QPDSALVRQARAERWSQWSLRGGMEMLPQTLHTYLTSRGVSVLKGQPVCGLTLQAEGHWK
Xerus_inauris@P    QSDSALIRQAQAERWSQWSLRGGMEMLPQTLDAYLTSRGVSVLRGQPVCGLTLQAEGRWK
Marmota_monax@P    QPDSALIRQARAERWSQWSLRGGMETLPQTLDTYLTSRGVSVLRGQPVCGLSLQAEGHWK
Spermophilus_da    QPDSALIRQARAERWSQWSLRGGMETLPQTLDTYLTSRGVSVLRGQPVCGLSLQAEGHWK
Ictidomys_tride    QPDSALIRQARAERWSQWSLRGGMETLPQTLDTYLTSRGVSILRGQPVCGLSLQAEGHWK
Urocitellus_par    QPDSALIRQARAERWSQWSLRGGMETLPQTLDTYLTSRGVSVLRGQPVCGLSLQAEGHWK
Sciurus_vulgari    QPDSALIRQARAERWSQWSLRGGMEMLPQTLDTYLTSNGVSVLRGQPVCGLTLQAEGHWK
Sciurus_carolin    QPDSALIRQARAERWSQWSLRGGMEMLPQTLDTYLTSNGVSVLRGQPVSGLTLQAEGHWK
Sciurus_niger@P    QPDSALIRQARAERWSQWSLRGGMEMLPQTLDTYLTSNGVSVLRGQPVSGLTLQAEGHWK
                   *.**:*:***:***********.* ***:*. .:*:*.**::* ****.**:**.**:**


Ppox               VSLGDSSLEADHIISAIPASELSKLLPAEAAPLARILSTIKAVSVAVVNLQYRGACLPV-
Aplodontia_rufa    VSLGDSSLEADHIISAIPASELSKLLPAEAAPLAHILSTITAVSVAVVNLQYRGARLPV-
Xerus_inauris@P    VSLGDSSLEADHIISAIPASELSKLLPMEAAPLAQVLSTITAVSVAVVNLQYQGARLPVQ
Marmota_monax@P    VSLGDSSLEADHIISAIPASELSKLLPTEAAPLAQVLNTITAVSVAVVNLQYRGARLPVQ
Spermophilus_da    VSLGDSSLEADHIISAIPASELSKLLPTEAAPLAQVLNTITAVSVAVVNLQYRGARLPV-
Ictidomys_tride    VSLGDSSLEADHIISAIPASELSKLLPTEAAPLAQVLNNITAVSVAVVNLQYRGACLPVQ
Urocitellus_par    VSLGDSSLEADHIISAIPASELSKLLPTEAAPLAQVLNTITAVSVAVVNLQYRGARLPV-
Sciurus_vulgari    VSLGDSSLEADHIISAIPASELSKLLPAEAAPLARILSTIKAVSVAVVNLQYRGACLPL-
Sciurus_carolin    VSLGDSSLEADHIISAIPASELSKLLPAEAAPLARILSTIKAVSVAVVNLQYRGACLPL-
Sciurus_niger@P    VSLGDSSLEADHIISAIPASELSKLLPAEAAPLARILSTIKAVSVAVVNLQYRGACLPL-
                   ************************** ******::*..*.*.***********:** **:


Ppox               ----------------------QGFGHLVPSSEDPTVLGIVYDSVAFPEQDGNPPSLR
Aplodontia_rufa    ----------------------QGFGHLVPSSEDPGVLGIVYDSVAFPEQDGSSPGLR
Xerus_inauris@P    VYWRGKEGIDSDGTFPSFFFFFPLQGFGHLVPSSEDPGVLGIVYDSVAFPEQDGSPPGLR
Marmota_monax@P    VYRGEKKVPQMEFFLLI-FFFFPLQGFGHLVPSSEDPGVLGIVYDSVAFPEQDGSPPGLR
Spermophilus_da    ----------------------QGFGHLVPSSEDPGVLGIVYDSVAFPEQDGSPPGLR
Ictidomys_tride    VYGGGKKGVASDGVFPS-YFFFSLQGFGHLVPSSEDPGVLGIVYDSVAFPEQDGSSPGLR
Urocitellus_par    ----------------------QGFGHLVPSSEDPGVLGIVYDSVAFPEQDGSPPGLR
Sciurus_vulgari    ----------------------QGFGHLVPSSEDPGVLGIVYDSVAFPEQDGSPPGLR
Sciurus_carolin    ----------------------QGFGHLVPSSEDPGVLGIVYDSVAFPEQDGNPPGLR
Sciurus_niger@P    ----------------------QGFGHLVPSSEDPGVLGIVYDSVAFPEQDGNPPGLR
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                              ************ ***************..*.**
Ppox             VT-------------------------------VMLGGYWLQKLKAAGHQLSPELFQQQ
Aplodontia_rufa  VTVRA----------------------------GGYWLQKLKAAGHQLSPELFQQQ
Xerus_inauris@P  VTVRAGHVVWAFQRALLCPVVGKAKLVSAIF-APVMLGGSWLQMLEASGCVLSQELFQQQ
Marmota_monax@P  VTVRAGHVVWAFQRALLCSIVGKAKLVSAIFPSQVMLGGSWLQTLEASGCVLSQELFQKQ
Spermophilus_da  VTVRAGHFVWAFQRALFCPIVGKAKLVSAIFPSQVMLGGSWLQTLEASGYVLSRELFQQQ
Ictidomys_tride  VTVRAGHVVWAFQRTLFCPIVGKAKLVSAIFPSQVMLGGSWLQTLEASGCVLSQELFQQQ
Urocitellus_par  VTVRAGHVVWAFQRALFCPIVGKAKLVSPIFPSQVMLGGSWLQTLEASGCVLSQELFQQQ
Sciurus_vulgari  VTVRAGHVVRVFQRAPLCPIVGKTKLVSAIFPSQVMLGGSWLQMLEASGCVLSQKLFQQQ
Sciurus_carolin  VTVRAGHVVRVFQRAPLCPIVGKAKLVSAIFPPQVMLGGSWLQMLEASDCVLSQKLFQQQ
Sciurus_niger@P  VTVRAGHVVRVFQRAPLCPTVGKAKLVSAIFPPQVMLGGSWLQMLEASGCVLSQKLFQQQ
                 **                                  ** *** *:*:.   ** :***:*

Ppox             AQEAAATQLGLKEPPSHCLVHLHK------------------------------------
Aplodontia_rufa  AQEAAATQLGLKEPPSHCLVHLHQ------------------------------------
Xerus_inauris@P  AQEAVATQLGLKEPPSHCLVHLHK------------------------------------
Marmota_monax@P  AQEAVATQLGLKEPPSHCLVHLHKVSWGKFLSVPCCRPCIQGIFVTVCQPRPGKSIINFI
Spermophilus_da  AQEAVATQLGLKEPPSHCLVHLHKVSWGKFLSVPYCRPCIQGIFVTVCQPRPGKSIINFI
Ictidomys_tride  AQEAVATQLGLKEPPSHCLVHLHK------------------------------------
Urocitellus_par  AQEAVATQLGLKEPPSHCLVHLHKVSWGKFLSVPYCRPCIQGIFVTVCQPRPGKSIINFI
Sciurus_vulgari  AQEAVATQLGLKEPPSHCLVHLHKVSWGKLISVPFLRP-IQGIFVILC-PRPGKSVINFV
Sciurus_carolin  AQEAVATQLGLKEPPSHCLVHLHKVSWGKLISVPFWRP-IQGIFVTVC-PRPGKSVINFV
Sciurus_niger@P  AQEAVATQLGLKEPPSHCLVHLHKVSWGKLISVPFWRP-IQGIFVTLC-PRPGKSVINFV
                 ****.*****************:

Ppox             --------NCIPQYTIGHWQK-----------------------LDSAMQFLTAQRL
Aplodontia_rufa  --------NCIPQYTLGHWQKLGKLGKLGGGQRKSDL-KLHSFHPFLPESAMKFLSAQKL
Xerus_inauris@P  --------NCIPQYTLGHWQKLGKLGKQLGELRKSDLQPQNSFHPFLLESAMKFLAAQRL
Marmota_monax@P  LYPLSSSQNCIPQYTLGHWQK-----------------------LESAMKFLAAQRL
Spermophilus_da  LYPLSSSQNCIPQYTLGHWQK-----------------------LESAMKFLAAQRL
Ictidomys_tride  --------NCIPQYTLGHWQKLGKVGKQLGGLRK-DL-PQNSFYSFLLESAMKFLAAQRL
Urocitellus_par  LYPLSSSQNCIPQYTLGHWQKLGKVGKQLGGLRK-DL-PQNSFYSFLLESAMKFLGAQRL
Sciurus_vulgari  LYSLPSSQNCIPQYTLGHWQKLGKFGKQLGGLKKSDL-PQNSFYPFLPESAMKFLAAQKL
Sciurus_carolin  LYPLPSSQNCIPQYTLGHWQKLGKFGKQLGGLKKSDL-PQNSFHPFLPESAMKFLAAQKL
Sciurus_niger@P  LYPLPSSQNCIPQYTLGHWQKLGKFGKQLGGLKKSDL-PQNSFHPFLPESAMKFLAAQKL
                        *******:*****                       :***:** **:*

Ppox             PLTLAGASYEGVAVNDCIESGRQAAVAVLGTESNSZ
Aplodontia_rufa  PLTLAGASYEGVAVNDCIESGRQAAVSVLGTESNS-
Xerus_inauris@P  PLTLAGASYEGVAVNDCIESGRQAAISVLGPESNS-
Marmota_monax@P  PLTLAGASYEGVAVNDCIESGRQAAISVLGPESNS-
Spermophilus_da  PLTLAGASYEGVAVNDCIESGRQAAISVLGPESNS-
Ictidomys_tride  PLTLAGASYEGVAVNDCIESGRQAAISVLGPESNS-
Urocitellus_par  PLTLAGASYEGVAVNDCIESGRQAAISVLGPESNS-
Sciurus_vulgari  PLTLAGASYEGVAVNDCIESGRQAAISVLGPESN--
Sciurus_carolin  PLTLAGASYEGVAVNDCIESGRQAAISVLGPES---
Sciurus_niger@P  PLTLAGASYEGVAVNDCIESGRQAAISVLGPESN--
                 ************************::***.**
```

UROD encodes uroporphyrinogen decarboxylase. Diseases associated with *UROD* include porphyria cutanea tarda and familial porphyria cutanea tarda. Among its related pathways are biosynthesis of cofactors and metabolism. Gene ontology (GO) annotations related to this gene include uroporphyrinogen decarboxylase activity. This gene encodes an enzyme responsible for catalyzing the conversion of uroporphyrinogen to coproporphyrinogen through the removal of

four carboxymethyl side chains. Mutations and deficiency in this enzyme are known to cause familial porphyria cutanea tarda and hepatoerythropoetic porphyria.

Within a 426-amino acid *UROD* sequence for *S. niger*, we observed nine point-differences among sciurids, including one contiguous tract of six where the *S. niger* sequence differed from those of *S. vulgaris* and *S. carolinensis*. *S. carolinensis* had a deletion of 38 amino acids relative to the sequences of *S. vulgaris* and *S. niger*. Comparing among all species, we observed insertions of 15 and 15 amino acids in *A. rufa* and 50 in *S. dauricus* and *U. parryii*.

```
Urod              MEANGFGLQNFPELKNDTFLRAAWGEETDYTPVWCMRQAGRYL------P---------
Aplodontia_rufa   --------QTFPELKNDTFLRAAWGEETDYTPVWCMRQAGRYLPGQGQGPEVINCVC---
Xerus_inauris@U   --------QSFPELKNDTFLRAAWGQETDYTPVWCMRQAGRYLPGQGQGP----------
Marmota_monax@U   --------QNFPELKNDTFLRAAWGEETDYTPVWCMRQAGRYL------P----------
Spermophilus_da   --------QNFPELKNDTFLRAAWGEETDYTPVWCMRQAGRYL------P----------
Ictidomys_tride   --------QNFPELKNDTFLRAAWGEETDYTPVWCMRQAGRYL------P----------
Urocitellus_par   --------QNFPELKNDTFLRAAWGEETDYTPVWCMRQAGRYL------P----------
Sciurus_vulgari   --------QSFPELKNDTFLRAAWGEETDYTPVWCMRQAGRYLPGEGQGPEFITLGSGGW
Sciurus_carolin   --------QSFPELKNDTFLRAAWGEETDYTPVWCMRQAGRYLPGQGQGPEFITLGSGGW
Sciurus_niger@U   --------QSFPELKNDTFLRAAWGEETDYTPVWCMRQAGRYLPGQGQGPEFITLGSGGW
                          * .*************:*****************        *

Urod              ---------------EFRETRAAQDFFSTCRSPEACCELT------------------
Aplodontia_rufa   -MSRASRLRSVFLLFAEFRKTRATQDFFSTCRSPEACCELT------------------
Xerus_inauris@U   ---------------EFRETRAAQDFFSTCRSPEACCELTLQVRGPEREVFMPSAYRLP
Marmota_monax@U   ---------------EFRETRATQDFFSTCRSPEACCELTLQVRGPQREVFMPTACHLA
Spermophilus_da   ---------------EFRETRATQDFFSTCRSPEACCELTLQVRSPQREVFMPSACHLA
Ictidomys_tride   ---------------EFRETRATQDFFSTCRSPEACCELTLQVRGPQREVFMPSACHLA
Urocitellus_par   ---------------EFRETRATQDFFSTCRSPEACCELTLQVRGPQREVFMPSACHLA
Sciurus_vulgari   GGALGARLRSAFLLSAEFRETRATQDFFSTCRSPEACCELTLQVRGPQREVFMSSACHLA
Sciurus_carolin   GGALGARLRSAFLLSAEFRETRATQDFFSTCRSPEACCELT------------------
Sciurus_niger@U   GGALGARLRSAFLLSAEFRETRATQDFFSTCRSPEACCELT------------------
                                  ***:***:*****************

Urod              -----LQPLRRFPLDAAIIFSDILVVPQALGMEVTMVPGKGPSFPEPLREERDLERLRDP
Aplodontia_rufa   -----LQPLRRFPLDAAIIFSDILVVPQALGLEVTMEPGKGPSFPEPLREERDLERLRDP
Xerus_inauris@U   TCFHSLQPLRRFPLDAAIIFSDILVVPQALGMEVIMVPGKGPSFPEPLREERDLERLRDP
Marmota_monax@U   TRFHSLQPLRRFPLDAAIIFSDILVVPQALGMEVTMVPGKGPSFPEPLREERDLERLRDP
Spermophilus_da   TRFHSLQPLRRFPLDAAIIFSDILVVPQALGMEVTMVPGKGPSFPEPLREERDLERLRDP
Ictidomys_tride   TRFHSLQPLRRFPLDAAIIFSDILVVPQALGMEVTMVPGKGPSFPEPLREERDLERLRDP
Urocitellus_par   TRFHSLQPLRRFPLDAAIIFSDILVVPQALGMEVTMVPGKGPSFPEPLREERDLERLRDP
Sciurus_vulgari   TCFHSLQPLRRFPLDAAIIFSDILVVPQALGMEVTMVPGKGPSFSEPLREEQDLERLRDP
Sciurus_carolin   -----LQPLRRFPLDAAIIFSDILVVPQALGMEVTMVPGKGPSFSEPLREERDLERLRDP
Sciurus_niger@U   -----LQPLRRFPLDAAIIFSDILVVPQALGMEVTMVPGKGPSFSEPLREERDLERLRDP
                       ***************************:** * *******.******:********

Urod              AAAASELGYVFQAITLTRQRLAGRVPLIGFAGAP------------------------
Aplodontia_rufa   AAVASELNYVFQAITLTRQQLAGRVPLIGFAGAPVIWEEQGLGHEITLADLVLTREGGVS
Xerus_inauris@U   SVVASELGYVFQAITLTRQQLAGRVPLIGFAGAP------------------------
Marmota_monax@U   EVVTSELGYVFQAITLTRQQLAGRVPLIGFAGAP------------------------
Spermophilus_da   EVVTSELGYVFQAITLTRQQLAGRVPLIGFAGAPVIWEKQGIGALWHI--WSRGRKCQCG
Ictidomys_tride   EVVTSELGYVFQAITLTRQQLAGRVPLIGFAGAPVIWEKQGTGALWHI--WCRGRKCECG
Urocitellus_par   EVVTSELGYVFQAITLTRQQLAGRVPLIGFAGAPVTWEKQGIGALWHI--WCRGRKCQCG
Sciurus_vulgari   AVVASELGYVFQAITLTRQQLAGRVPLIGFAGAPVIWDKQGTGTDHAG--ISSIDKGSVN
Sciurus_carolin   AVVASELGYVFQAITLTRQQLAGRVPLIGFAGAP------------------------
Sciurus_niger@U   AVVASELGYVFQAITLTRQQLAGRVPLIGFAGAPVTWDKQGTGADHAG--VSSIDKGSVS
                    ..:***.***********:***************
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```
Urod                ------------WTLMTYMVEGGSSSTMAQAKRWLYQRPQASHKLLGILTDVLVPYLIGQ
Aplodontia_rufa     LTSALHLYILL-WTLMTYMVEGGSSSTMAQSKRWLYQRPQASHKLLGILTDALVPYLVGQ
Xerus_inauris@U     ------------WTLMTYMVEGGSSSTMAQSKRWLYQRPQASHQLLRILTDALVPYLVGQ
Marmota_monax@U     ------------WTLMTYMVEGGSSSTMAQSKRWLYQRPQASHQLLRILTDALVPYLVGQ
Spermophilus_da     FCTVTSL-ILLQWTLMTYMVEGGSSSTMAQSKRWLYQRPQASHQLLRILTDALVPYLVGQ
Ictidomys_tride     FCTVTSL-ILLQWTLMTYMVEGGSSSTMAQSKRWLYQRPQASHQLLRILTDALVPYLVGQ
Urocitellus_par     FCTVTSL-ILLQWTLMTYMVEGGSSSTMAQSKRWLYQRPQASHQLLRILTDALVPYLVGQ
Sciurus_vulgari     VASALRLCILLQWTLMTYMVEGGSSSTMAQSKRWLYQRPQASHQLLRILTDVLVPYLI--
Sciurus_carolin     ------------WTLMTYMVEGGSSSTMAQSKRWLYQRPQASHQLLRILTDVLVPYLI--
Sciurus_niger@U     VASALHLCILLQWTLMTYMVEGGSSSTMAQSKRWLYQRPQASHQLLRILTDALVPYLVGQ
                                **********.******:*************:** ****.*****:

Urod                VAAGA-QALQLFESHAGHLGTELFSKFALPYIRDVAKRVKAGLQKAGLAPVPM-------
Aplodontia_rufa     VPRQVPRHCSSFESHAGHLGTELFSKFALPYIRDVAKRVKAGLQKAGLAPVPM-------
Xerus_inauris@U     VAAGA-QALQLFESHAGHLGPQLFNKFSLPYIRDVAKRVKARLQEAGLAPVPM-------
Marmota_monax@U     VAAGA-QALQLFESHAGHLGPQLFNKFALPYIRDVAKRVKARLQEAGLAPVPM-------
Spermophilus_da     VAAGA-QALQLFESHAGHLGPQLFNKFALPYIRDVAKRVKARLQEAGLAPVPMVRIGIGW
Ictidomys_tride     VAAGA-QALQLFESHAGHLGPQLFNKFALPYIRDVAKRVKARLQEAGLAPVPM-------
Urocitellus_par     VAAGA-QALQLFESHAGHLGPQLFNKFALPYIRDVAKRVKARLQEAGLAPVPMVRIGIGW
Sciurus_vulgari     FFTTL-LALQLFESHAGHLGPQLFSKFALPYIRDVAKRVKAKLQEAGLAPVPM-------
Sciurus_carolin     FFTTL-LALQLFESHAGHLGPQLFSKFALPYIRDVAKRVKAKLQEAGLAPVPM-------
Sciurus_niger@U     VAAGA-QALQLFESHAGHLGPQLFSKFALPYIRDVAKRVKAKLQEAGLAPVPM-------
                    .          . *********.:**.**:************* **:********

Urod                -----------------------------------------------IIFAKDGHFALEELAQ
Aplodontia_rufa     -----------------------------------------------IIFAKDGHFALEELAQ
Xerus_inauris@U     -----------------------------------------------IIFAKDGHFALEELAQ
Marmota_monax@U     -----------------------------------------------IIFAKDGHFALEELAQ
Spermophilus_da     WVCRVFRVSLAWTEVTTGGQQKCIQERLVGTARPYVSQIRFFLQIIFAKDGHFALEELAQ
Ictidomys_tride     -----------------------------------------------IIFAKDGHFALEELAQ
Urocitellus_par     WVCRVFRVSHAWTEVTTGGQQKCIQERLVGTARPYVSQILFFLQIIFAKDGHFALEELAQ
Sciurus_vulgari     -----------------------------------------------IIFAKDGHFALEELAQ
Sciurus_carolin     -----------------------------------------------IIFAKDGHFALEELAQ
Sciurus_niger@U     -----------------------------------------------IIFAKDGHFALEELAQ
                                                                    ***************

Urod                AGYEVVGLDWTVAPKKARERVGKAVTLQGNLDPCALYASEEEIGRLVQQMLDDFGPQRYI
Aplodontia_rufa     AGYEVVGLDWTVAPKKARERVGKMVTLQGNLDPCALYASEEEIGRLVKQMLDDFGPQHYI
Xerus_inauris@U     AGYEVVGLDWTMAPKKARERVGKTVTLQGNLDPCALYASEEEIGRLVQQMLDDFGPQRYI
Marmota_monax@U     AGYEVVGLDWTVAPKKARERVGKSVTLQGNLDPCALYASEEEIGRLVQQMLDDFGPKRYI
Spermophilus_da     AGYEVVGLDWTVAPKKARERVGKSVTLQGNLDPCALYASEEEIGRLVQQMLDDFGPKRYI
Ictidomys_tride     AGYEVVGLDWTVAPKKARERVGKSVTLQGNLDPCALYASEEEIGRLVQQMLDDFGPKRYI
Urocitellus_par     AGYEVVGLDWTVAPKKARERVGKSVTLQGNLDPCALYASEEEIGQLVQQMLDDFGPKRYI
Sciurus_vulgari     AGYEVVGLDWTVAPKKARERVGKTVTLQGNLDPCALYASEEEIGQMVQKMLDDFGPQRYI
Sciurus_carolin     AGYEVVGLDWTVAPKKARERVGKTVTLQGNLDPCALYASEEEIGQMVQKMLDDFGPQRYI
Sciurus_niger@U     AGYEVVGLDWTVAPKKARERVGKTVTLQGNLDPCALYASEEEIGQMVQKMLDDFGPQRYI
                    ***********:*********** ********************::*::*******::**

Urod                ANLGHGLYPDMDPERVGAFVDAVHKHSRLLRQNZ
Aplodontia_rufa     ANLGHGLYPDMDPEHVGAFVDAVHRHSRLLRQN-
Xerus_inauris@U     ANLGHGLYPDMDPEHVGAFVDAVHRHSRLLRQN-
Marmota_monax@U     ANLGHGLYPDMDPEHVGAFVDAVHRHSRLLRQN-
Spermophilus_da     ANLGHGLYPDMDPEHVGAFVDAVHRHSRLLRQN-
Ictidomys_tride     ANLGHGLYPDMDPEHVGAFVDAVHRHSRLLRQN-
Urocitellus_par     ANLGHGLYPDMDPEHVGAFVDAVHRHSRLLRQN-
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Sciurus_vulgari ANLGHGLYPDMDPEHVGAFVDAVHRHSRLLRQN-
Sciurus_carolin ANLGHGLYPDMDPEHVGAFVDAVHRHSRLLRQN-
Sciurus_niger@U ANLGHGLYPDMDPEHVGAFVDAVHRHSRLLRQN-
                **************:*********:*******
```

UROS encodes uroporphyrinogen III synthase. Diseases associated with *UROS* include porphyria and congenital erythropoietic and cutaneous porphyria, or Gunther's disease. Among its related pathways are porphyrin metabolism and biosynthesis of cofactors. Gene ontology (GO) annotations related to this gene include cofactor binding and uroporphyrinogen-III synthase activity. The protein encoded by this gene catalyzes the fourth step of porphyrin biosynthesis in the heme biosynthetic pathway. The human UROS protein has 199 amino acids before any squirrel one. *M. monax, S. dauricus, I. tridecemlineatus*, and *U. parryii* had an 11-amino acid sequence not similar to the human sequence. From amino acid 419, the sequences of all species were similar. The *S. niger* amino acid sequence differed from those of *S. vulgaris* and *S. carolinensis* at amino acid 229, and the *S. carolinensis* sequence from those of *S. vulgaris* and *S. niger* at amino acid 256.

```
Uros            MKVLLLKDAKEDDSGLDPYIQELRLCGLEATLIPVLSFEFMSLPSLSEKLSHPEGFGGLI
Aplodontia_rufa ------------------------------------------------------------
Xerus_inauris@U ------------------------------------------------------------
Marmota_monax@U ------------------------------------------------------------
Spermophilus_da ------------------------------------------------------------
Ictidomys_tride ------------------------------------------------------------
Urocitellus_par ------------------------------------------------------------
Sciurus_vulgari ------------------------------------------------------------
Sciurus_carolin ------------------------------------------------------------
Sciurus_niger@U ------------------------------------------------------------


Uros            FTSPRAVEAVKLCLEKDNKTEAWEKSLKDRWNAKSVYVVGSATASLVNKIGLDAEGAGSG
Aplodontia_rufa ------------------------------------------------------------
Xerus_inauris@U ------------------------------------------------------------
Marmota_monax@U ------------------------------------------------------------
Spermophilus_da ------------------------------------------------------------
Ictidomys_tride ------------------------------------------------------------
Urocitellus_par ------------------------------------------------------------
Sciurus_vulgari ------------------------------------------------------------
Sciurus_carolin ------------------------------------------------------------
Sciurus_niger@U ------------------------------------------------------------


Uros            NAEKLAEYICSKPSSELPLLFPCGTIKGDTLPKMLKDKGIPMESMHVYQTVPHPGIQGSL
Aplodontia_rufa ------------------------------------------------------------
Xerus_inauris@U ------------------------------------------------------------
Marmota_monax@U ------------------------------------------------------------
Spermophilus_da ------------------------------------------------------------
Ictidomys_tride ------------------------------------------------------------
Urocitellus_par ------------------------------------------------------------
Sciurus_vulgari ------------------------------------------------------------
Sciurus_carolin ------------------------------------------------------------
Sciurus_niger@U ------------------------------------------------------------
```

```
Uros              KSYYEDQGIPASITFFSPSGLKYSLEYIQALSGSSFDQIKFIAIGPSTTRAMAAKGLPVS
Aplodontia_rufa   ------------------------------------QFAAIGPSTARALAAKGLPVS
Xerus_inauris@U   -------------------------------SSLPSLQFAAIGPTTARALTSKGLPVS
Marmota_monax@U   -----------------GVMYRKALAEA---LSLPSLQFAAIGPTTAHALTAKGLPVS
Spermophilus_da   -----------------GVMYRKALAEA---LSLPSLQFAAIGPTTAHALTAKGLPVS
Ictidomys_tride   -----------------GVMYQKALAEA---LSLPSLQFAAIGPTTAHALTAKGLPVS
Urocitellus_par   -----------------GVTYRKALAEA---LSLPSLQFAAIGPTTAHALTAKGLPVS
Sciurus_vulgari   -------------------------------SSLPSSQFAAIGPTTARALAAQGLPVS
Sciurus_carolin   ----------------------------------FAAIGPTTARALAAQGLPVS
Sciurus_niger@U   ------------------------------SLSSSQFAAIGPTTARTLAAQGLPVS
                                                * ****:*:::::::*****

Uros              CTAESPTPQALAAGIRNVLKPNHCCZ
Aplodontia_rufa   CTAESPTPQALAASIRKALQPHSCC-
Xerus_inauris@U   CTAESPTPQALAAGIRKALQPQGCC-
Marmota_monax@U   CTAESPTPQALAAGIRKALQPQGCC-
Spermophilus_da   CTAESPTPQALAAGIRKALQPQGCC-
Ictidomys_tride   CTAESPTPQALAAGIRKALQPQGCC-
Urocitellus_par   CTAESPTPQALAAGIRKALQPQGCC-
Sciurus_vulgari   CTAESPTPQALAAGIRKALQPQ----
Sciurus_carolin   CTAESPTPQALAAGIWKALQPQGSC-
Sciurus_niger@U   CTAESPTPQALAAGIRKALQPQGSC-
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